(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 October 2004 (14.10.2004)

PCT

(10) International Publication Number
WO 2004/087120 A2

(51) International Patent Classification[7]: A61K 31/00

(21) International Application Number:
PCT/GB2004/001286

(22) International Filing Date: 23 March 2004 (23.03.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0307333.5 29 March 2003 (29.03.2003) GB

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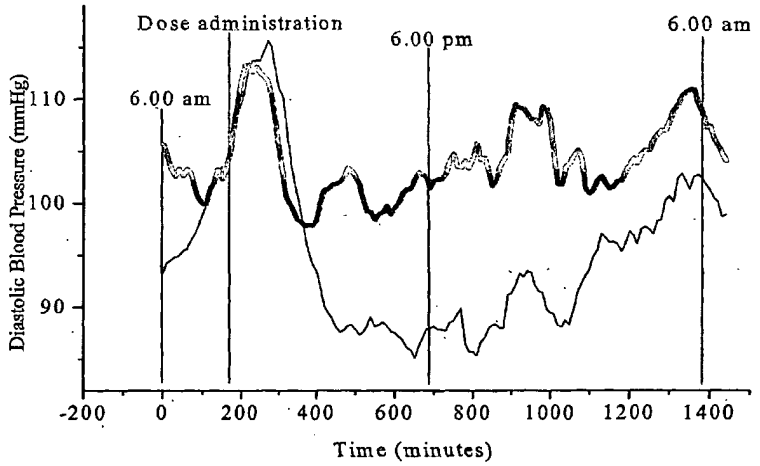
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH,

[Continued on next page]

(54) Title: THERAPEUTIC AGENT



effect of Src-5 on rat diastolic blood pressure

(57) Abstract: The invention relates to the use of a Src kinase inhibitor in the production of a medicament for use in the prophylaxis or treatment of hypertension. More particularly, the invention concerns the anti-hypertensive use of a selective Src kinase inhibitor that possess less potent VEGF receptor tyrosine kinase inhibitory properties. The invention also relates to a combination product comprising a Src kinase inhibitor and one or more further anti-hypertensive agents and to the use of Src kinase inhibitors as primary regulators of cardiovascular disease and in the prevention of stroke.

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GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

THERAPEUTIC AGENT

This invention relates to a novel therapeutic agent, in particular the invention relates to the use as a hypotensive agent of a compound that is an inhibitor of one of more of the members of the Src family of non-receptor tyrosine kinase enzymes, or a pharmaceutically-acceptable salt thereof. The invention also concerns the use of such a compound in the production of a medicament for use in the prophylaxis or treatment of hypertension. The invention further concerns a method of treating hypertension which comprises the administration of an effective amount of such a compound to a warm-blooded animal such as man.

Hypertension is a prevalent cardiovascular disorder that affects many millions of people which, despite the availability of several classes of anti-hypertensive agents, remains an important cause of patient morbidity and mortality. Accordingly, there is a continuing need for the discovery and use of further classes of anti-hypertensive agent to expand the armamentarium of medicines available to the medical practitioner in order to increase the chance that control of hypertension may be achieved. We have made the surprising discovery that compounds that are inhibitors of one of more of the members of the Src family of non-receptor tyrosine kinase enzymes are useful for the control of hypertension when administered alone or in combination with a known anti-hypertensive agent.

Src Non-Receptor Tyrosine Kinase Inhibition

In recent years it has been discovered that cells may become cancerous by virtue of the transformation of a portion of its DNA into an oncogene *i.e.* a gene which, on activation, leads to the formation of malignant tumour cells. It is known, for example, that several oncogenes encode tyrosine kinase enzymes and that certain growth factor receptors are also tyrosine kinase enzymes. The first group of tyrosine kinases to be identified arose from such viral oncogenes, for example $pp60^{v\text{-}Src}$ tyrosine kinase (otherwise known as v-Src) and the corresponding tyrosine kinases in normal cells, for example $pp60^{c\text{-}Src}$ tyrosine kinase (otherwise known as c-Src).

The Src family of non-receptor tyrosine kinases is located intracellularly and is involved in the transmission of biochemical signals such as those that influence tumour cell motility, dissemination and invasiveness and subsequently metastatic tumour growth. Members of the Src family include *inter alia* c-Src, c-Yes, c-lck and c-Fyn.

It is further known that the Src family of non-receptor tyrosine kinases is highly regulated in normal cells such that, in the absence of extracellular stimuli, the kinases are maintained in an inactive conformation. However, some Src family members, for example c-Src tyrosine kinase, are frequently significantly activated (when compared to normal cell levels) in common human cancers.

Accordingly it has been recognised that an inhibitor of such non-receptor tyrosine kinases should be of value as a selective inhibitor of the motility of tumour cells and as a selective inhibitor of the dissemination and invasiveness of mammalian cancer cells leading to inhibition of metastatic tumour growth.

Linkage of Growth Factor Receptors to Blood Pressure Effects

A complex interaction of a number of mediators leads to the strict control of blood pressure in the normal mammal. The system is such that if the level of one mediator changes the resultant effect is compensated for by the other mediators such that normal blood pressure is maintained (Guyton *et al.*, Annual Review of Physiology, 1972, 34, 13-46, and Quan *et al.*, Pacing and Clinical Electrophysiology, 1997, 20, 764-774). It is important that blood pressure is tightly controlled because hypertension underlies a variety of cardiovascular diseases such as stroke, acute myocardial infarction and renal failure.

Many substances exhibit effects on blood vessels *in vitro* which, in isolation, would suggest effects on blood pressure *in vivo*. However, because of the nature of the compensation mechanisms that control blood pressure, it is often the case that anticipated *in vivo* effects are not obtained and thus normal blood pressure is maintained. It has been reported that various growth factor receptors may be involved as mediators in the control of blood pressure in the normal mammal.

(a) Blood Pressure Effects of VEGF Receptor Tyrosine Kinases

Angiogenesis is stimulated via the promotion of the growth of endothelial cells. Several polypeptides with *in vitro* endothelial cell growth promoting activity have been identified including acidic and basic fibroblast growth factors (aFGF & bFGF) and vascular endothelial growth factor (VEGF). By virtue of the restricted expression of its receptors, the growth factor activity of VEGF is relatively specific towards endothelial cells. Recent evidence indicates that VEGF is an important stimulator of both normal and pathological angiogenesis (Jakeman *et al.*, Endocrinology, 1993, 133, 848-859; Kolch *et al.*, Breast Cancer Research and Treatment, 1995, 36, 139-155) and vascular permeability (Connolly *et al.*, J. Biol. Chem., 1989, 264, 20017-20024). Alteration of vascular permeability is also thought to play a role in both normal and

pathological physiological processes (Senger *et al.*, Cancer and Metastasis Reviews, 1993, 12, 303-324).

VEGF binds to a receptor with intrinsic tyrosine kinase activity, a so-called receptor tyrosine kinase (RTK). One RTK family comprises the *fms*-like tyrosine kinase receptor Flt or Flt1, the kinase insert domain-containing receptor KDR (also referred to as Flk-1) and the *fms*-like tyrosine kinase receptor Flt4. Two of these related RTKs, namely Flt and KDR, have been shown to bind VEGF with high affinity (De-Vries *et al.*, Science, 1992, 255, 989-991; Terman *et al.*, Biochem. Biophys. Res. Comm., 1992, 187, 1579-1586). Binding of VEGF to these receptors expressed in heterologous cells has been associated with changes in the tyrosine phosphorylation status of cellular proteins and calcium fluxes.

Antagonism of the activity of VEGF is expected to be beneficial in the treatment of a number of disease states that are associated with angiogenesis and/or increased vascular permeability such as cancer.

Compounds which are inhibitors of VEGF receptor tyrosine kinase are described in, for example, International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856, WO 97/34876, WO 97/42187, WO 98/13354, WO 98/13350, WO 99/10349, WO 00/21955, WO 00/47212 and WO 01/32651.

It has been reported that VEGF and FGF have acute effects on vascular tone. VEGF has been shown to dilate dog coronary arteries *in vitro* (Ku *et al.*, Amer. J. Physiology, 1993, 265, H585-H592) and to induce hypotension in the conscious rat (Yang *et al.*, J. Cardiovascular Pharmacology, 1996, 27, 838-844). However, *in vivo* the effects of these agents are only transitory. Even with a very large dose of VEGF (250 μg/kg) in conscious rats, Yang *et al.* observed a return to normal blood pressure within 20 minutes. At lower doses of VEGF, blood pressure returned to normal significantly faster. A similar effect was observed in anaesthetised rats with the blood pressure returning to normal within 30 minutes of the administration of 15 μg/kg bFGF (Boussairi *et al.*, J. Cardiovascular Pharmacology, 1994, 23, 99-102). These studies also showed that tachyphylaxis (or desensitisation) quickly develops following growth factor administration. Thus, further administration of growth factor has no effect on blood pressure.

It has been reported that the vasodilation induced by both FGF and VEGF depends, at least in part, on the release of nitric oxide (Morbidelli *et al.*, Amer. J. Physiology, 1996, 270, H411-H415 and Wu *et al.*, Amer. J. Physiology, 1996, 271, H1087-H1093).

The complexity and confusion as to the effect of VEGF on blood pressure is illustrated by the following two patent applications that disclose contrasting effects.

A method for treating a hypertensive disorder in a pregnant woman is described in International Patent Application WO 98/28006, the method comprising administering an amount of a therapeutic substance which regulates the amount and/or activity of VEGF. Thus, according to this disclosure, a VEGF RTK inhibitor may be expected to reduce blood pressure.

However, a method for treating essential hypertension is described in International Patent Application WO 00/13703, the method comprising administering to a patient an effective amount of an angiogenic factor such as VEGF, or an agonist thereof. Thus, according to this disclosure, a VEGF RTK inhibitor may be expected to increase blood pressure.

More recently, it has been disclosed in International Patent Application WO 01/74360 that VEGF receptor tyrosine kinase inhibitors, provided that they possess suitable pharmacokinetic properties which provide reasonable bioavailability, do lead to a sustained increase in blood pressure when administered to rats, particularly when administered chronically.

(b) Blood Pressure Effects of Src Non-Receptor Tyrosine Kinase

As with the initial studies of the effect of VEGF on blood pressure, there is complexity and confusion as to the effect of Src kinase on blood pressure as illustrated by the following two groups of disclosures.

On the one hand, it has been disclosed in various papers concerning the *in vitro* electrophysiologic effects of tyrosine kinases including c-Src kinase that tyrosine kinase enzymatic activity can be involved in the movement of calcium ions across cellular membranes (Wijetunge *et al.*, Biochem. Biophys. Res. Comm., 1992, 189, 1620-1623, Biochem. Biophys. Res. Comm., 1995, 217, 1039-1044 and British Journal of Pharmacology, 1998, 124, 307-316 and Hu *et al.*, Journal of Biological Chemistry, 1998, 273, 5337-5342). However, there has been no disclosure of the relevance of such *in vitro* effects of Src kinase on blood pressure control *in vivo* in a warm-blooded animal such as man.

In contrast, it has been disclosed in International Patent Application WO 99/61590 that Src kinase may be used to modulate the angiogenesis in tissues caused by 'angiogenic molecules' such as bFGF. As discussed hereinbefore, VEGF is another 'angiogenic molecule'. In addition, it has been disclosed by Cheresh *et al.*, in Nature Medicine, 2001, 7, 222-227, and

International Patent Application WO 01/45751, that the angiogenesis factor VEGF is produced in response to ischaemic injury, for example cerebral ischaemia (stroke) in the brain. It was disclosed that VEGF alone did not cause an increase in vascular permeability leading to brain oedema and tissue damage but that Src kinase activity regulates (*i.e.* controls) the ability of VEGF to increase vascular permeability and that a Src kinase inhibitor could block vascular permeability. Using animal studies, it was disclosed that the administration of the Src inhibitor PP1 reduced infarct volume following cerebral ischaemia and that there was no direct effect on cerebral blood flow. It was asserted that Src kinase inhibition may be useful to prevent secondary damage following a stroke and may also 'impact the course of other ischemic diseases such as myocardial infarction'.

If Src kinase activity does control the effectiveness of VEGF, it might be reasonable to expect that a Src kinase inhibitor, when administered chronically, would have a similar effect on blood pressure as a VEGFR tyrosine kinase inhibitor *i.e.* a hypertensive effect (as disclosed in International Patent Application WO 01/74360).

The present invention

We have surprisingly now found that an inhibitor of one of more of the members of the Src family of non-receptor tyrosine kinase enzymes when administered to a warm-blooded animal causes a decrease in blood pressure. In particular, we have found that a selective Src kinase inhibitor when administered to a warm-blooded animal causes a substantial decrease in blood pressure. More particularly, we have found that a selective Src kinase inhibitor that possesses pharmacokinetic properties which provide a reasonable bioavailability when administered chronically to a warm-blooded animal causes a sustained decrease in blood pressure.

According to a first aspect of the present invention there is provided the use of a compound that is an inhibitor of one of more of the members of the Src family of non-receptor tyrosine kinase enzymes (hereinafter Src kinase), or a pharmaceutically-acceptable salt thereof, in the production of a medicament for use in the prophylaxis or treatment of hypertension.

A suitable compound that is a Src kinase inhibitor is a compound that, in general, possesses one or more of :-

(i) an IC_{50} value against Src kinase in the range, for example, 0.001 to 5μM, preferably in the range, for example, 0.001 to 0.5μM;

(ii) greater inhibitory potency against Src kinase than against VEGF receptor kinases; and

(iii) pharmacokinetic properties which provide a reasonable bioavailability when administered to a warm-blooded animal, especially when administered chronically.

Compounds which possess Src kinase inhibitory properties are described in, for example, International Patent Applications WO 01/94341, WO 02/16352, WO 02/30924, WO 02/30926, WO 02/34744, WO 02/085895, WO 02/092577, WO 02/092578, WO 02/092579 and WO 03/008409 and in co-pending International Application PCT/GB03/04703 (that arose from European Patent Application No. 02292736.2).

It is disclosed in Journal Medicinal Chemistry, 2001, 44, 822-833 and 3965-3977 that certain 4-anilino-3-cyanoquinoline derivatives are useful for the inhibition of Src-dependent cell proliferation. The 4-anilino-3-cyanoquinoline Src inhibitor known as SKI 606 is described in Cancer Research, 2003, 63, 375.

Other compounds which possess Src kinase inhibitory properties are described in, for example, International Patent Applications WO 96/10028, WO 97/07131, WO 97/08193, WO 97/16452, WO 97/28161, WO 97/32879 and WO 97/49706.

Other compounds which possess Src kinase inhibitory properties are described in, for example, International Patent Application WO 03/013540, particularly the compounds disclosed therein by way of Formulae I to VIII and compounds based on Formulae VII and VIII but wherein the 2,6-dimethylphenyl group is replaced by a 2,6-dichlorophenyl or a 2-chloro-6-methylphenyl group.

Other compounds which possess Src kinase inhibitory properties are described in, for example, J Bone Mineral Research, 1999, 14 (Suppl. 1), S487, Molecular Cell, 1999, 3, 639-647, Journal Medicinal Chemistry, 1997, 40, 2296-2303, Journal Medicinal Chemistry, 1998, 41, 3276-3292 and Bioorganic & Medicinal Chemistry Letters, 2002, 12, 1361 and 3153.

Particular Src kinase inhibitors include :-

(i) 4-amino-5-(3-methoxyphenyl)-7-{4-[2-(2-methoxyethylamino)ethoxy]phenyl}-pyrrolo[2,3-*d*]pyrimidine and 4-amino-5-(3-methoxyphenyl)-7-(4-{2-[di-(2-methoxyethyl)amino]ethoxy}phenyl)pyrrolo[2,3-*d*]pyrimidine which are obtainable by methods described in International Patent Application WO 96/10028;

(ii) 4-amino-7-*tert*-butyl-5-(4-tolyl)pyrazolo[3,4-*d*]pyrimidine which is also known as PP1 and is described in Molecular Cell, 1999, 3, 639-648;

(iii) 2-(2,6-dichloroanilino)-6,7-dimethyl-1,8-dihydroimidazo[4,5-*h*]isoquinolin-9-one and 2-(2,6-dichloroanilino)-7-[(E)-3-diethylaminoprop-1-enyl]-6-methyl-1,8-dihydroimidazo[4,5-*h*]isoquinolin-9-one which are obtainable by methods described in Journal Medicinal Chemistry, 2002, 45, 3394;

(iv) 1-[6-(2,6-dichlorophenyl)-2-(4-diethylaminobutyl)pyrido[2,3-*d*]pyrimidin-7-yl]-3-ethylurea which is obtainable by methods described in Journal Medicinal Chemistry, 1997, 40, 2296-2303 and Journal Medicinal Chemistry, 2001, 44, 1915;

(v) 6-(2,6-dichlorophenyl)-2-[4-(2-diethylaminoethoxy)anilino]-8-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one which is also known as PD166285 and is described in J. Pharmacol. Exp. Ther., 1997, 283, 1433-1444;

(vi) the compound known as PD162531 which is described in Mol. Biol. Cell, 2000, 11, 51-64; and

(vii) the compound known as PD173955 which is described in Cancer Research, 1999, 59, 6145-6152.

Other compounds which may possess Src kinase inhibitory properties are described in, for example, International Patent Applications WO 02/079192, WO 03/000188, WO 03/000266, WO 03/000705, WO 02/083668, WO 02/092573, WO 03/004492, WO 00/49018, WO 03/013541, WO 01/00207, WO 01/00213 and WO 01/00214.

According to this aspect of the present invention there is also provided the use of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, in the production of a medicament for use in the prophylaxis or treatment of hypertension wherein the Src kinase inhibitor possesses selective Src kinase inhibitory properties.

Suitable selective Src kinase inhibitors for use in the present invention possess potent inhibitory activity against the Src family of non-receptor tyrosine kinases, for example by inhibition of c-Src and/or c-Yes, whilst possessing less potent inhibitory activity against other tyrosine kinase enzymes such as the receptor tyrosine kinases, in particular against VEGF receptor tyrosine kinases such as the *fms*-like tyrosine kinase receptor Flt and the kinase insert domain-containing receptor KDR that have been shown to bind VEGF with high affinity. Furthermore, suitable selective Src kinase inhibitors for use in the present invention possess substantially better potency against the Src family of non-receptor tyrosine kinases, for example c-Src and/or c-Yes, than against VEGF receptor tyrosine kinases such that they may be used in an amount sufficient to inhibit, for example, c-Src and/or c-Yes whilst possessing little activity against the VEGF receptor tyrosine kinases. Such selectivity is beneficial for the

anti-hypertensive activity of the present invention given that it has been disclosed in International Patent Application WO 01/74360 that VEGF receptor tyrosine kinase inhibitors lead to a sustained increase in blood pressure when administered chronically. Compounds exhibiting such Src selectivity provide a greater degree of hypotension than those which possess significant VEGF receptor tyrosine kinase inhibitory activity.

Thus, according to this aspect of the present invention there is also provided the use of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, in the production of a medicament for use in the prophylaxis or treatment of hypertension wherein the Src kinase inhibitor possesses substantially better potency against the Src family of non-receptor tyrosine kinases than against VEGF receptor tyrosine kinases.

The potency of a Src kinase inhibitor may be assessed using a conventional Elisa assay such as that described in, for example, International Patent Application WO 01/94341. The activity of a Src kinase inhibitor against VEGF receptor tyrosine kinases such as Flt and KDR may also be assessed using appropriate conventional assays such as those described in, for example, International Patent Application WO 98/13354. In general, a Src kinase inhibitor according to the present invention possesses a Src kinase IC_{50} in the range, for example, 0.001 - 1 μM and a KDR IC_{50} in the range, for example, 0.1 - 100 μM. The selectivity of the Src kinase activity of a test compound may be assessed by dividing the KDR IC_{50} by the Src kinase IC_{50} to provide a ratio. When it is stated that the Src kinase inhibitor possesses substantially better potency against Src kinase than against VEGF receptor tyrosine kinases, this means that the ratio of KDR IC_{50} to Src kinase IC_{50} is :-

(i) in general, in the range, for example, of about 5 to 10,000;

(ii) particularly, in the range, for example, of about 25 to 10,000; and

(iii) preferably, in the range, for example, of about 100 to 10,000.

Suitable compounds which possess such selective Src kinase inhibitory properties are described in, for example, International Patent Applications WO 01/94341, WO 02/16352, WO 02/30924, WO 02/30926, WO 02/34744, WO 02/085895, WO 02/092577, WO 02/092578, WO 02/092579 and WO 03/008409 and in co-pending International Application PCT/GB03/04703 (that arose from European Patent Application No. 02292736.2).

Particular selective Src kinase inhibitors that may be used in the prophylaxis or treatment of hypertension are described in, for example, International Patent Applications WO 01/94341 and WO 02/16352 and in co-pending International Application PCT/GB03/04703 (that arose from European Patent Application No. 02292736.2).

Further particular Src kinase inhibitors that may be used in the prophylaxis or treatment of hypertension include those Src kinase inhibitors that possess appropriate pharmacokinetic properties after administration to a warm-blooded animal such as a rat, dog or human, particularly after oral administration. Such compounds provide suitable blood levels and a reasonable bioavailability when administered acutely, particularly when administered chronically. In general, a Src kinase inhibitor as defined hereinbefore will be administered chronically over a number of days to allow the patient's hypertension to be brought under control. In general, oral administration is preferred, particularly using a tablet form.

According to this aspect of the present invention there is provided the use of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, in the production of a medicament for chronic administration for the prophylaxis or treatment of hypertension.

In general, a Src kinase inhibitor that possesses suitable pharmacokinetic properties when administered to a warm-blooded animal such as man possesses one or more of the following pharmacokinetic parameters :-

(i) Compound Clearance of less than about 75% of hepatic blood flow (hepatic blood flow in the human is about 25 ml/min/kg, in the dog is about 35 ml/min/kg and in the rat is about 75 ml/min/kg);

(ii) a Volume of Distribution of less than about 30 L/kg;

(iii) a bioavailability of more than about 20%; and

(iv) an elimination half life in the range, for example, of about 0.2 to 15 hours.

In general, a particular Src kinase inhibitor that possesses suitable pharmacokinetic properties when administered to a warm-blooded animal such as man possesses one or more of the following pharmacokinetic parameters :-

(i) Compound Clearance of less than about 50% of hepatic blood flow;

(ii) a Volume of Distribution of less than about 20 L/kg;

(iii) a bioavailability of more than about 30%; and

(iv) an elimination half life in the range, for example, of about 0.5 to 10 hours.

In general, a more particular Src kinase inhibitor that possesses suitable pharmacokinetic properties when administered to a warm-blooded animal such as man possesses one or more of the following pharmacokinetic parameters :-

(i) Compound Clearance of less than about 40% of hepatic blood flow;

(ii) a Volume of Distribution of less than about 10 L/kg;

(iii) a bioavailability of more than about 40%; and

(iv) an elimination half life in the range, for example, of about 1 to 7.5 hours.

According to this aspect of the present invention there is also provided the use of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, in the production of a medicament for chronic administration for the prophylaxis or treatment of hypertension wherein the Src kinase inhibitor possesses substantially better potency against the Src family of non-receptor tyrosine kinases than against VEGF receptor tyrosine kinases.

Particular selective Src kinase inhibitors that may be used for chronic administration for the prophylaxis or treatment of hypertension are described in, for example, International Patent Applications WO 01/94341 and WO 02/16352 and in co-pending International Application PCT/GB03/04703 (that arose from European Patent Application No. 02292736.2).

Particular Src kinase inhibitors include the following compounds from International Patent Application WO 01/94341 :-

4-(2-chloro-5-methoxyanilino)-5,7-di-(3-morpholinopropoxy)quinazoline,

4-(2-bromo-5-methoxyanilino)-7-methoxy-5-(N-methylpiperidin-4-yloxy)quinazoline,

4-(2-chloro-5-methoxyanilino)-7-methoxy-5-(N-methylpiperidin-4-yloxy)quinazoline,

4-(2-chloro-5-methoxyanilino)-7-[3-(4-methylpiperazin-1-yl)propoxy]-5-tetrahydropyran-4-yloxyquinazoline,

4-(2-chloro-5-methoxyanilino)-7-(3-morpholinopropoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(2-chloro-5-methoxyanilino)-7-[2-hydroxy-3-(4-methylpiperazin-1-yl)propoxy]-5-tetrahydropyran-4-yloxyquinazoline,

4-(2-chloro-5-methoxyanilino)-7-(2-hydroxy-3-morpholinopropoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(2-chloro-5-methoxyanilino)-7-[3-(4-methylpiperazin-1-yl)propoxy]-5-tetrahydrofuran-3-yloxyquinazoline,

4-(2-chloro-5-methoxyanilino)-7-(3-morpholinopropoxy)-5-tetrahydrofuran-3-yloxyquinazoline,

4-(5-chloronaphth-1-ylamino)-7-methoxy-5-(N-methylpiperidin-4-yloxy)quinazoline,

4-(3-chlorobenzofuran-7-ylamino)-7-methoxy-5-(N-methylpiperidin-4-yloxy)quinazoline,

7-benzyloxy-4-(2-bromo-5-methoxyanilino)-5-piperidin-4-yloxyquinazoline,

4-(2-bromo-5-methoxyanilino)-7-(3-methylsulphonylpropoxy)-5-piperidin-4-yloxyquinazoline,

4-(2-bromo-5-methoxyanilino)-7-methoxy-5-piperidin-4-ylmethoxyquinazoline,

4-(2,4-dichloro-5-methoxyanilino)-7-methoxy-5-(N-methylpiperidin-4-yloxy)quinazoline,

4-(2,5-dimethoxyanilino)-7-methoxy-5-(N-methylpiperidin-4-yloxy)quinazoline,

4-(2,4-dichloro-5-methoxyanilino)-7-(2-pyrrolidin-1-ylethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(2,4-dichloro-5-methoxyanilino)-7-(2-piperidinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(2,4-dichloro-5-methoxyanilino)-7-(2-morpholinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(2,4-dichloro-5-methoxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline,

4-(2-bromo-5-methoxyanilino)-7-(2-pyrrolidin-1-ylethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(2-bromo-5-methoxyanilino)-7-(2-piperidinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(2-bromo-5-methoxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline,

4-(2-bromo-5-methoxyanilino)-7-(4-pyridyloxyethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(2-bromo-5-methoxyanilino)-7-{2-[(2S)-2-(N,N-dimethylcarbamoyl)pyrrolidin-1-yl]ethoxy}-5-tetrahydropyran-4-yloxyquinazoline,

4-(2-bromo-5-methoxyanilino)-7-{2-[(2S)-2-(N-methylcarbamoyl)pyrrolidin-1-yl]ethoxy}-5-tetrahydropyran-4-yloxyquinazoline,

4-(2-bromo-5-methoxyanilino)-7-(4-pyridylmethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(5-methoxy-2-pyrrolidin-1-ylanilino)-7-[3-(4-methylpiperazin-1-yl)propoxy]-5-tetrahydropyran-4-yloxyquinazoline,

4-(2-bromo-5-methoxyanilino)-5-cyclopentyloxy-7-(2-pyrrolidin-1-ylethoxy)quinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-5-cyclopentyloxy-7-(2-pyrrolidin-1-ylethoxy)quinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-5-piperidin-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-methoxy-5-piperidin-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-methoxy-5-(N-methylpiperidin-4-yloxy)quinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-methoxy-5-piperidin-4-ylmethoxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-(2-pyrrolidin-1-ylethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-(3-pyrrolidin-1-ylpropoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-[3-(4-methylpiperazin-1-yl)propoxy]-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-(2-piperidinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-pyridyloxy)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-piperidin-4-ylmethoxy-5-tetrahydropyran-4-yloxyquinazoline and

4-(6-chloro-2,3-methylenedioxyanilino)-7-(N-methylpiperidin-4-ylmethoxy)-5-tetrahydropyran-4-yloxyquinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

Further particular Src kinase inhibitors include the following compounds from International Patent Application WO 02/16352 :-

6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-morpholinopropoxy)quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-[3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy]quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-piperidinopropoxy)quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-(N-methylpiperidin-4-ylmethoxy)quinazoline,

7-(2-hydroxy-3-pyrrolidin-1-ylpropoxy)-6-methoxy-4-(2,3-methylenedioxyanilino)-quinazoline,

7-[2-hydroxy-3-(N-isopropyl-N-methylamino)propoxy]-6-methoxy-4-(2,3-methylenedioxyanilino)quinazoline,

7-[3-(4-cyanomethylpiperazin-1-yl)-2-hydroxypropoxy]-6-methoxy-4-(2,3-methylenedioxyanilino)quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-{2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy}quinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-[3-(4-cyanomethylpiperazin-1-yl)propoxy]-6-methoxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,

4-(6-bromo-2,3-methylenedioxyanilino)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-[2-(N-methylpiperidin-4-yl)ethoxy]quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-[2-(4-pyridyloxy)ethoxy]quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-pyridylmethoxy)quinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-(2-cyanopyrid-4-ylmethoxy)-6-methoxyquinazoline and

4-(6-chloro-2,3-methylenedioxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

Further particular Src kinase inhibitors include the following compounds from International Patent Application WO 02/30924 :-

4-(7-benzofuranylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,

4-(7-benzofuranylamino)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,

4-(7-benzofuranylamino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,

4-(7-benzofuranylamino)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,

4-(3-chlorobenzofuran-7-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,

4-(3-chlorobenzofuran-7-ylamino)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,

4-(3-chlorobenzofuran-7-ylamino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,

4-(3-chlorobenzofuran-7-ylamino)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,

4-(6-chlorobenzofuran-7-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,

4-(6-chlorobenzofuran-7-ylamino)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,

4-(6-chlorobenzofuran-7-ylamino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,

4-(6-chlorobenzofuran-7-ylamino)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,

4-(5-fluorobenzofuran-7-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,

4-(5-fluorobenzofuran-7-ylamino)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,

4-(5-fluorobenzofuran-7-ylamino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,

4-(5-fluorobenzofuran-7-ylamino)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,

4-(7-benzofuranylamino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline,

7-(2-acetoxy-3-pyrrolidin-1-ylpropoxy)-4-(3-chlorobenzofuran-7-ylamino)-6-methoxyquinazoline,

7-[2-acetoxy-3-(N-isopropyl-N-methylamino)propoxy]-4-(3-chlorobenzofuran-7-ylamino)-6-methoxyquinazoline,

7-[2-acetoxy-3-(4-cyanomethylpiperazin-1-yl)propoxy]-4-(3-chlorobenzofuran-7-ylamino)-6-methoxyquinazoline,

7-(2-acetoxy-3-piperidinopropoxy)-4-(3-chlorobenzofuran-7-ylamino)-6-methoxyquinazoline,

4-(3-chlorobenzofuran-7-ylamino)-7-(2-hydroxy-3-pyrrolidin-1-ylpropoxy)-6-methoxyquinazoline,

4-(3-chlorobenzofuran-7-ylamino)-7-[2-hydroxy-3-(N-isopropyl-N-methylamino)propoxy]-6-methoxyquinazoline,

4-(3-chlorobenzofuran-7-ylamino)-7-[3-(4-cyanomethylpiperazin-1-yl)-2-hydroxypropoxy]-6-methoxyquinazoline and

4-(3-chlorobenzofuran-7-ylamino)-7-(2-hydroxy-3-piperidinopropoxy)-6-methoxyquinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

Further particular Src kinase inhibitors include the following compounds from International Patent Application WO 02/30926 :-

4-(4-benzofuranylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,

4-(4-benzofuranylamino)-7-[3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy]-6-methoxyquinazoline,

4-(4-benzofuranylamino)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,

4-(4-benzofuranylamino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,

4-(4-benzofuranylamino)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,

4-(4-benzofuranylamino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline,
4-(5-chlorobenzofuran-4-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
7-(2-acetoxy-3-pyrrolidin-1-ylpropoxy)-4-(3-chlorobenzofuran-4-ylamino)-
6-methoxyquinazoline,
7-[2-acetoxy-3-(N-isopropyl-N-methylamino)propoxy]-4-(3-chlorobenzofuran-4-ylamino)-
6-methoxyquinazoline,
7-[2-acetoxy-3-(4-cyanomethylpiperazin-1-yl)propoxy]-4-(3-chlorobenzofuran-4-ylamino)-
6-methoxyquinazoline,
7-(2-acetoxy-3-piperidinopropoxy)-4-(3-chlorobenzofuran-4-ylamino)-6-methoxyquinazoline,
7-(2-acetoxy-3-morpholinopropoxy)-4-(3-chlorobenzofuran-4-ylamino)-
6-methoxyquinazoline,
4-(4-benzofuranylamino)-7-(2-hydroxy-3-pyrrolidin-1-ylpropoxy)-6-methoxyquinazoline,
4-(4-benzofuranylamino)-7-[2-hydroxy-3-(N-isopropyl-N-methylamino)propoxy]-
6-methoxyquinazoline,
4-(4-benzofuranylamino)-7-[3-(4-cyanomethylpiperazin-1-yl)-2-hydroxypropoxy]-
6-methoxyquinazoline,
4-(4-benzofuranylamino)-7-(2-hydroxy-3-piperidinopropoxy)-6-methoxyquinazoline and
4-(4-benzofuranylamino)-7-(2-hydroxy-3-morpholinopropoxy)-6-methoxyquinazoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

Further particular Src kinase inhibitors include the following compounds from International Patent Application WO 02/34744 :-

4-(7-indolylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
4-(2,3-dimethylindol-7-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
7-[3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy]-4-(7-indolylamino)-
6-methoxyquinazoline,
4-(7-indolylamino)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,
4-(7-indolylamino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,
4-(7-indolylamino)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,
4-(3-chloroindol-7-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
4-(7-indolylamino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline,
7-(2-acetoxy-3-pyrrolidin-1-ylpropoxy)-4-(3-chloroindol-7-ylamino)-6-methoxyquinazoline,
7-[2-acetoxy-3-(N-isopropyl-N-methylamino)propoxy]-4-(3-chloroindol-7-ylamino)-
6-methoxyquinazoline,

7-[2-acetoxy-3-(4-cyanomethylpiperazin-1-yl)propoxy]-4-(3-chloroindol-7-ylamino)-6-methoxyquinazoline,

7-(2-acetoxy-3-piperidinopropoxy)-4-(3-chloroindol-7-ylamino)-6-methoxyquinazoline,

7-(2-acetoxy-3-morpholinopropoxy)-4-(3-chloroindol-7-ylamino)-6-methoxyquinazoline,

4-(3-chloroindol-7-ylamino)-7-(2-hydroxy-3-pyrrolidin-1-ylpropoxy)-6-methoxyquinazoline,

4-(3-chloroindol-7-ylamino)-7-[2-hydroxy-3-(N-isopropyl-N-methylamino)propoxy]-6-methoxyquinazoline,

4-(3-chloroindol-7-ylamino)-7-[3-(4-cyanomethylpiperazin-1-yl)-2-hydroxypropoxy]-6-methoxyquinazoline,

4-(3-chloroindol-7-ylamino)-7-(2-hydroxy-3-piperidinopropoxy)-6-methoxyquinazoline and

4-(3-chloroindol-7-ylamino)-7-(2-hydroxy-3-morpholinopropoxy)-6-methoxyquinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

Further particular Src kinase inhibitors include the following compounds from International Patent Application WO 02/085895 :-

6-methoxy-4-(2,3-methylenedioxyphenoxy)-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,

4-(6-chloro-2,3-methylenedioxyphenoxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,

4-(6-bromo-2,3-methylenedioxyphenoxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,

6-methoxy-4-(2,3-methylenedioxyphenoxy)-7-(3-morpholinopropoxy)quinazoline,

4-(6-chloro-2,3-methylenedioxyphenoxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,

4-(6-bromo-2,3-methylenedioxyphenoxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,

6-methoxy-4-(2,3-methylenedioxyphenoxy)-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,

4-(6-chloro-2,3-methylenedioxyphenoxy)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,

4-(6-bromo-2,3-methylenedioxyphenoxy)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,

6-methoxy-4-(2,3-methylenedioxyphenoxy)-7-(3-methylsulphonylpropoxy)quinazoline,

4-(6-chloro-2,3-methylenedioxyphenoxy)-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline and

4-(6-bromo-2,3-methylenedioxyphenoxy)-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

Further particular Src kinase inhibitors include the following compounds from International Patent Application WO 02/092577 :-

4-(2-chloro-5-methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline,

4-(2-chloro-5-methoxyanilino)-6-methoxy-7-piperidin-4-ylmethoxyquinazoline and

4-(2-bromo-5-methoxyanilino)-6-methoxy-7-[2-(N-methylpiperidin-4-yl)ethoxy]quinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

Further particular Src kinase inhibitors include the following compounds from International Patent Application WO 02/092578 :-

4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline,

4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-piperidin-4-ylmethoxyquinazoline,

4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-[2-(N-methylpiperidin-4-yl)ethoxy]quinazoline and

4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-(2-piperidin-4-ylethoxy)quinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

Further particular Src kinase inhibitors include the following compounds from International Patent Application WO 02/092579 :-

4-(2-chloro-5-methoxyanilino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,

4-(2-chloro-5-methoxyanilino)-6-methoxy-7-(2-piperidinoethoxy)quinazoline and

4-(2-chloro-5-methoxyanilino)-6-methoxy-7-(2-morpholinoethoxy)quinazoline and

4-(2-bromo-5-methoxyanilino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline

or a pharmaceutically-acceptable acid-addition salt thereof.

Further particular Src kinase inhibitors include the following compounds from International Patent Application WO 03/008409 :-

4-(6-chloro-2,3-methylenedioxyanilino)-3-cyano-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-(3-chloropropoxy)-3-cyano-6-methoxyquinoline,

4-(6-chloro-2,3-methylenedioxyanilino)-3-cyano-7-methoxy-5-(N-methylpiperidin-4-yloxy)quinoline,

4-(6-chloro-2,3-methylenedioxyanilino)-3-cyano-7-(2-pyrrolidin-1-ylethoxy)-5-tetrahydropyran-4-yloxyquinoline,

4-(6-chloro-2,3-methylenedioxyanilino)-3-cyano-7-(3-pyrrolidin-1-ylpropoxy)-5-tetrahydropyran-4-yloxyquinoline,

4-(6-chloro-2,3-methylenedioxyanilino)-3-cyano-7-[3-(4-methylpiperazin-1-yl)propoxy]-5-tetrahydropyran-4-yloxyquinoline,

4-(6-chloro-2,3-methylenedioxyanilino)-3-cyano-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinoline,

4-(6-chloro-2,3-methylenedioxyanilino)-3-cyano-7-(2-piperidinoethoxy)-5-tetrahydropyran-4-yloxyquinoline and

4-(6-chloro-2,3-methylenedioxyanilino)-3-cyano-7-(N-methylpiperidin-4-ylmethoxy)-5-tetrahydropyran-4-yloxyquinoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

Further particular Src kinase inhibitors include the following compounds from co-pending International Application PCT/GB03/04703 (that arose from European Patent Application No. 02292736.2) :-

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-methoxy-7-[3-(4-prop-2-ynylpiperazin-1-yl)propoxy]quinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-[3-(4-isobutyrylpiperazin-1-yl)propoxy]-6-methoxyquinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-methoxy-7-{3-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]propoxy}quinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-methoxy-7-[2-(4-prop-2-ynylpiperazin-1-yl)ethoxy]quinazoline,

7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-tetrahydropyran-4-yloxyquinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-{2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline,

7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxyquinazoline and

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-{2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl)ethoxy]-5-isopropoxyquinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

More particular selective Src kinase inhibitors include the following compounds :-

4-(2,4-dichloro-5-methoxyanilino)-7-(2-piperidinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(2,4-dichloro-5-methoxyanilino)-7-(2-morpholinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(2,4-dichloro-5-methoxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline,

4-(2-bromo-5-methoxyanilino)-7-(2-pyrrolidin-1-ylethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-(2-pyrrolidin-1-ylethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-(3-pyrrolidin-1-ylpropoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-[3-(4-methylpiperazin-1-yl)propoxy]-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-(2-piperidinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-morpholinopropoxy)quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-[3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy]quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-piperidinopropoxy)quinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-[3-(4-isobutyrylpiperazin-1-yl)propoxy]-6-methoxyquinazoline,

4-(2-chloro-5-methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline,

4-(2-chloro-5-methoxyanilino)-6-methoxy-7-piperidin-4-ylmethoxyquinazoline,

4-(2-bromo-5-methoxyanilino)-6-methoxy-7-[2-(N-methylpiperidin-4-yl)ethoxy]quinazoline,

4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline,

4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-piperidin-4-ylmethoxyquinazoline,

4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-[2-(N-methylpiperidin-4-yl)ethoxy]quinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-methoxy-7-[3-(4-prop-2-ynylpiperazin-1-yl)propoxy]quinazoline,

7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-tetrahydropyran-4-yloxyquinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-{2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline,

7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxyquinazoline and

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-{2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl)ethoxy]-5-isopropoxyquinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

Preferred selective Src kinase inhibitors include the following compounds :-

4-(2,4-dichloro-5-methoxyanilino)-7-(2-piperidinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(2,4-dichloro-5-methoxyanilino)-7-(2-morpholinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-(2-pyrrolidin-1-ylethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-(3-pyrrolidin-1-ylpropoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-(2-piperidinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-morpholinopropoxy)quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-piperidinopropoxy)quinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-[3-(4-isobutyrylpiperazin-1-yl)propoxy]-6-methoxyquinazoline,

4-(2-chloro-5-methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline,

4-(2-chloro-5-methoxyanilino)-6-methoxy-7-piperidin-4-ylmethoxyquinazoline,
4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline,
4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-piperidin-4-ylmethoxyquinazoline,
7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-tetrahydropyran-4-yloxyquinazoline,
4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-{2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline,
7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxyquinazoline and
4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-{2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl)ethoxy]-5-isopropoxyquinazoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

A particular preferred selective Src kinase inhibitor for use in the invention is 4-(6-chloro-2,3-methylenedioxyanilino)-7-(2-pyrrolidin-1-ylethoxy)-5-tetrahydropyran-4-yloxyquinazoline, or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular preferred selective Src kinase inhibitor for use in the invention is 4-(6-chloro-2,3-methylenedioxyanilino)-7-(3-pyrrolidin-1-ylpropoxy)-5-tetrahydropyran-4-yloxyquinazoline, or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular preferred selective Src kinase inhibitor for use in the invention is 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline, or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular preferred selective Src kinase inhibitor for use in the invention is 4-(6-chloro-2,3-methylenedioxyanilino)-7-(2-piperidinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline, or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular preferred selective Src kinase inhibitor for use in the invention is 6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-morpholinopropoxy)quinazoline, or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular preferred selective Src kinase inhibitor for use in the invention is 6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-piperidinopropoxy)quinazoline, or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular preferred selective Src kinase inhibitor for use in the invention is 4-(6-chloro-2,3-methylenedioxyanilino)-7-[3-(4-isobutyrylpiperazin-1-yl)propoxy]-6-methoxyquinazoline, or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular preferred selective Src kinase inhibitor for use in the invention is 4-(2-chloro-5-methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline, or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular preferred selective Src kinase inhibitor for use in the invention is 7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-tetrahydropyran-4-yloxyquinazoline, or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular preferred selective Src kinase inhibitor for use in the invention is 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-{2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline, or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular preferred selective Src kinase inhibitor for use in the invention is 7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxyquinazoline, or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular preferred selective Src kinase inhibitor for use in the invention is 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-{2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl)ethoxy]-5-isopropoxyquinazoline, or a pharmaceutically-acceptable acid-addition salt thereof.

A suitable pharmaceutically-acceptable salt of a Src kinase inhibitor that is sufficiently basic is, for example, a pharmaceutically-acceptable acid-addition salt, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid. A suitable pharmaceutically-acceptable salt of a Src kinase inhibitor that is sufficiently acidic is, for example, a pharmaceutically-acceptable alkali or alkaline earth metal salt such as a calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

In order to use Src kinase inhibitors to provide an anti-hypertensive effect according to the present invention, the compounds may be administered in the form of a suitable pharmaceutical composition. The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including

intravenous, subcutaneous, intramuscular, intravascular or infusion) for example as a sterile solution, suspension or emulsion, for topical administration for example as an ointment or cream, for rectal administration for example as a suppository or the route of administration may be by direct injection into the tumour or by regional delivery or by local delivery. In other embodiments of the present invention the Src inhibitor may be delivered endoscopically, intratracheally, intralesionally, percutaneously, intravenously, subcutaneously or intraperitoneally. In general the compositions described herein may be prepared in a conventional manner using conventional excipients or carriers that are well known in the art.

Suitable pharmaceutically-acceptable excipients or carriers for a tablet formulation include, for example, inert excipients such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or alginic acid; binding agents such as gelatin or starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl 4-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid excipient, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. The compositions of the present invention are advantageously presented in unit dosage form. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 0.5 g of active agent (more suitably from 0.5 to 100 mg, for example from 1 to 30 mg) compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

A Src kinase inhibitor as defined hereinbefore will generally be administered chronically so that a daily dose in the range, for example, 0.02 mg/kg to 75 mg/kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a daily dose in the range, for example, 0.01 mg/kg to 30 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a daily dose in the range, for example, 0.01 mg/kg to 25 mg/kg body weight will be used. Oral administration is however preferred, particularly in tablet form, to provide a daily dose in the range, for example, 0.02 mg/kg to 15 mg/kg body weight, more preferably 0.02 mg/kg to 5 mg/kg body weight.

The dosages and schedules described hereinbefore may be varied according to the particular condition of the patient. For example, it may be necessary or desirable to reduce the above-mentioned dose of the Src kinase inhibitor in order to reduce toxicity. Dosages and schedules may also vary if, in addition to the Src kinase inhibitor, one or more additional anti-hypertensive agents are used. Scheduling can be determined by the practitioner who is treating any particular patient using his professional skill and knowledge.

According to a further aspect of the present invention there is provided a method for the prophylaxis or treatment of hypertension in a warm-blooded animal such as man which comprises the administration of an effective anti-hypertensive amount of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the present invention there is provided a method for providing an anti-hypertensive effect in a warm-blooded animal such as man which comprises the administration of an effective anti-hypertensive amount of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the present invention there is provided a method for the prophylaxis or treatment of hypertension that is sensitive to Src kinase inhibition which comprises the administration to a warm-blooded animal such as man of an effective anti-hypertensive amount of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the present invention there is provided a method for providing an anti-hypertensive effect in a warm-blooded animal such as man whose hypertension is sensitive to Src kinase inhibition which comprises the administration of an

effective anti-hypertensive amount of a compound that is a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the present invention there is also provided a method for the prophylaxis or treatment of hypertension in a warm-blooded animal such as man which comprises the administration of an effective anti-hypertensive amount of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore, wherein the Src kinase inhibitor possesses selective kinase inhibitory properties.

According to a further aspect of the present invention there is also provided a method for providing an anti-hypertensive effect in a warm-blooded animal such as man which comprises the administration of an effective anti-hypertensive amount of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore, wherein the Src kinase inhibitor possesses selective kinase inhibitory properties.

According to a further aspect of the present invention there is also provided a method for the prophylaxis or treatment of hypertension that is sensitive to Src kinase inhibition which comprises the administration to a warm-blooded animal such as man of an effective anti-hypertensive amount of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore, wherein the Src kinase inhibitor possesses selective kinase inhibitory properties.

According to a further aspect of the present invention there is also provided a method for providing an anti-hypertensive effect in a warm-blooded animal such as man whose hypertension is sensitive to Src kinase inhibition which comprises the administration of an effective anti-hypertensive amount of a compound that is a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore, wherein the Src kinase inhibitor possesses selective kinase inhibitory properties.

According to a further aspect of the present invention there is also provided a method for the prophylaxis or treatment of hypertension in a warm-blooded animal such as man which comprises the administration of an effective anti-hypertensive amount of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore, wherein the Src kinase inhibitor possesses substantially better potency against the Src family of non-receptor tyrosine kinases than against VEGF receptor tyrosine kinases.

According to a further aspect of the present invention there is also provided a method for providing an anti-hypertensive effect in a warm-blooded animal such as man which comprises the administration of an effective anti-hypertensive amount of a Src kinase

inhibitor, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore, wherein the Src kinase inhibitor possesses substantially better potency against the Src family of non-receptor tyrosine kinases than against VEGF receptor tyrosine kinases.

According to a further aspect of the present invention there is also provided a method for the prophylaxis or treatment of hypertension that is sensitive to Src kinase inhibition which comprises the administration to a warm-blooded animal such as man of an effective anti-hypertensive amount of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore, wherein the Src kinase inhibitor possesses substantially better potency against the Src family of non-receptor tyrosine kinases than against VEGF receptor tyrosine kinases.

According to a further aspect of the present invention there is also provided a method for providing an anti-hypertensive effect in a warm-blooded animal such as man whose hypertension is sensitive to Src kinase inhibition which comprises the administration of an effective anti-hypertensive amount of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore, wherein the Src kinase inhibitor possesses substantially better potency against the Src family of non-receptor tyrosine kinases than against VEGF receptor tyrosine kinases.

Particular selective Src kinase inhibitors that may be used in the prophylaxis or treatment of hypertension are described in, for example, International Patent Applications WO 01/94341 and WO 02/16352 and in co-pending International Application PCT/GB03/04703 (that arose from European Patent Application No. 02292736.2).

According to a further aspect of the present invention there is also provided a method for the prophylaxis or treatment of hypertension in a warm-blooded animal such as man which comprises the chronic administration of an effective anti-hypertensive amount of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the present invention there is also provided a method for providing an anti-hypertensive effect in a warm-blooded animal such as man which comprises the chronic administration of an effective anti-hypertensive amount of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the present invention there is also provided a method for the prophylaxis or treatment of hypertension that is sensitive to Src kinase inhibition which comprises the chronic administration to a warm-blooded animal such as man of an effective

anti-hypertensive amount of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the present invention there is also provided a method for providing an anti-hypertensive effect in a warm-blooded animal such as man whose hypertension is sensitive to Src kinase inhibition which comprises the chronic administration of an effective anti-hypertensive amount of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the present invention there is provided a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore for use in the prophylaxis or treatment of hypertension.

According to a further aspect of the present invention there is provided a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore for use in providing an anti-hypertensive effect.

Combinations

Hypertension may be controlled using a Src kinase inhibitor that is administered alone or in combination with one or more known anti-hypertensive agents. If a combination of a Src kinase inhibitor and one or more further anti-hypertensive agents are used, appropriate scheduling and appropriate dosages can be determined by the practitioner who is treating any particular patient using his professional skill and knowledge. Conveniently, each further anti-hypertensive agent may be administered at a conventional dose and by a conventional route. Typically, the individual daily dose of a further anti-hypertensive agent may be in the range from about one quarter of the minimum recommended dose to about the maximum recommended dose.

Suitable further anti-hypertensive agents include the many known categories of anti-hypertensive agents including calcium channel blockers, angiotensin converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor antagonists (A-II antagonists), beta-adrenergic receptor blockers (β-blockers), alpha-adrenergic receptor antagonists (α-antagonists), central alpha-adrenergic receptor agonists (α-agonists), vasodilators (including cerebral, coronary and peripheral vasodilators), thiazides and related diuretics, endothelin receptor antagonists and imidazoline I-agonists. Any drug from such categories of anti-hypertensive agent may be used in accordance with this invention. Suitable drugs from such categories of anti-hypertensive agent class are given hereinafter.

Suitable calcium channel blockers include amlodipine, diltiazem, verapamil, nifedipine and nisoldipine. Suitable ACE inhibitors include captopril, enalapril, lisinopril and ramipril. Suitable A-II antagonists include candesartan, irbesartan, losartan and valsartan. Suitable β-blockers include atenolol, carvedilol, celiprolol, metoprolol, propranolol and timolol. Suitable α-antagonists include doxazosin, prazosin and terazosin. Suitable central α-agonists include clonidine and methyldopa. Suitable vasodilators include diazoxide, dipyridamole, hydralazine and minoxidil. Suitable diuretics include benzothiadiazine derivatives, diuretic organomercurials, diuretic purines, diuretic steroids, diuretic sulfonamide derivatives and diuretic uracils, for example amiloride, isosorbide, bendroflumethazide, cyclopenthiazide, hydrochlorothiazide, hydroflumethiazide, polythiazide, acetazolamide, bumetanide and clopamide. Suitable endothelin receptor antagonists include bosentan. Suitable imidazoline I-agonists include moxonidine.

Preferred anti-hypertensive agents for use in a combination of a Src kinase inhibitor and a further anti-hypertensive agent include calcium channel blockers, A-II antagonists, ACE inhibitors and β-blockers.

According to this aspect of the present invention there is provided a combination product comprising a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore and one or more further anti-hypertensive agents as defined hereinbefore for use in the prophylaxis or treatment of hypertension.

It is to be understood that term "a combination product" envisages the simultaneous, separate or sequential administration of the components of the combination. In one aspect of the invention, "a combination product" envisages simultaneous administration of the Src kinase inhibitor and the further anti-hypertensive agent. In a further aspect of the invention, "a combination product" envisages sequential administration of those agents. In another aspect of the invention, "a combination product" envisages separate administration of those agents. Where the administration of those agents is sequential or separate, the delay in administering the second component should not be such as to lose the benefit of the effect of the combination therapy. Thus, for the avoidance of doubt, the present invention provides a combination product comprising a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, and a further anti-hypertensive agent for use simultaneously, sequentially or separately in the prophylaxis or treatment of hypertension.

The therapeutic combination of the present invention may be administered in the form of a suitable pharmaceutical composition. According to this aspect of the invention there is provided a pharmaceutical composition for use in the prophylaxis or treatment of hypertension which comprises a combination product as defined hereinbefore in association with a pharmaceutically-acceptable excipient or carrier.

It will be appreciated that the pharmaceutical composition according to this aspect of the present invention includes a composition comprising a Src kinase inhibitor as defined hereinbefore and a further anti-hypertensive agent as defined hereinbefore and a pharmaceutically-acceptable excipient or carrier. Such a composition conveniently provides the therapeutic combination product of the invention for simultaneous administration in the prophylaxis or treatment of hypertension.

A pharmaceutical composition according to this aspect of the present invention also includes separate compositions comprising a first composition comprising a Src inhibitor and a pharmaceutically-acceptable excipient or carrier, and a second composition comprising a further anti-hypertensive agent and a pharmaceutically-acceptable excipient or carrier. Such a composition conveniently provides the therapeutic combination product of the invention for sequential or separate administration in the prophylaxis or treatment of hypertension but the separate compositions may also be administered simultaneously.

Conveniently such a pharmaceutical composition of this aspect of the invention comprises a kit comprising a first container with a suitable composition containing the Src kinase inhibitor and a second container with a suitable composition containing a further anti-hypertensive agent. According to this aspect of the present invention there is provided a kit for use in the prophylaxis or treatment of hypertension comprising :-

a) a Src kinase inhibitor together with a pharmaceutically-acceptable excipient or carrier in a first unit dosage form;

b) a further anti-hypertensive agent together with a pharmaceutically-acceptable excipient or carrier in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to this aspect of the invention there is also provided a pharmaceutical composition for use in the prophylaxis or treatment of hypertension which comprises a combination product as defined hereinbefore in association with a pharmaceutically-acceptable excipient or carrier.

According to a further aspect of the present invention there is provided the use of a combination product as defined hereinbefore in the manufacture of a medicament for administration to a warm-blooded animal such as man to provide the prophylaxis or treatment of hypertension.

According to a further aspect of the present invention there is provided a method for the prophylaxis or treatment of hypertension which comprises the administration to a warm-blooded animal such as man that is in need of such treatment of effective anti-hypertensive amounts of the components of the combination product as defined hereinbefore.

According to this aspect of the present invention there is also provided a method for the prophylaxis or treatment of hypertension which comprises the administration to a warm-blooded animal such as man that is in need of such treatment of an effective anti-hypertensive amount of a Src kinase inhibitor as defined hereinbefore before, simultaneously with or after the administration of an effective anti-hypertensive amount of a further anti-hypertensive agent as defined hereinbefore before.

According to this aspect of the present invention there is also provided a method for the prophylaxis or treatment of hypertension which comprises the simultaneous, sequential or separate administration to a warm-blooded animal such as man that is in need of such treatment of effective anti-hypertensive amounts of the components of the combination product as defined hereinbefore.

According to this aspect of the present invention there is also provided a method for the prophylaxis or treatment of hypertension which comprises the administration to a warm-blooded animal such as man that is in need of such treatment of an effective anti-hypertensive amount of a Src inhibitor as defined hereinbefore and the simultaneous, sequential or separate administration of an effective anti-hypertensive amount of the further anti-hypertensive agent as defined hereinbefore.

As stated hereinbefore, it has been disclosed by Cheresh *et al.*, Nature Medicine, 2001, 7, 222-227, that Src kinase inhibition may be useful to prevent secondary damage following a stroke and may also 'impact the course of other ischemic diseases such as myocardial infarction'.

In another aspect of the present invention, we have surprisingly found that a Src kinase inhibitor is useful not only in the control of hypertension but also in the primary regulation of diseases of the cardiovascular system. As such, a Src kinase inhibitor is useful in attenuating

the primary damage that leads to cardiovascular disease such as heart disease (for example angina pectoris, cardiac arrythmia, congestive heart failure and ischaemic heart disease), renal failure and nephritis. In particular, a Src kinase inhibitor has wider activity than that contemplated by Cheresh *et al.* and its use need not be restricted to dosing only after a stroke or after a myocardial infarct.

In this aspect of the present invention, the use of a Src kinase inhibitor for 'the primary regulation of diseases of the cardiovascular system' means that a Src kinase inhibitor may be used for the prevention or treatment of diseases of the cardiovascular system. The phrase 'the primary regulation of diseases of the cardiovascular system' does not extend to or embrace 'secondary damage' that follows a stroke or that follows myocardial infarction.

According to this aspect of the present invention there is also provided the use of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, in the production of a medicament for chronic administration for the primary regulation of diseases of the cardiovascular system.

According to a further aspect of the present invention there is also provided a method for the primary regulation of diseases of the cardiovascular system in a warm-blooded animal such as man which comprises the chronic administration of an effective cardiovascular regulating amount of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

In another aspect of the present invention, we have surprisingly found that a Src kinase inhibitor is useful not only in the control of hypertension and in the primary regulation of diseases of the cardiovascular system but also in the prevention of brain disease such as stroke. In particular, a Src kinase inhibitor has wider activity than that contemplated by Cheresh *et al.* and its use need not be restricted to dosing only after a stroke.

In this aspect of the present invention, it is to be understood that the use of a Src kinase inhibitor for 'the prevention of brain disease such as stroke' means that the 'secondary damage' that follows a stroke is not embraced.

According to this aspect of the present invention there is also provided the use of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, in the production of a medicament for use in the prevention of brain disease such as stroke.

According to a further aspect of the present invention there is also provided a method for the prevention of brain disease such as stroke in a warm-blooded animal such as man

which comprises the administration of an effective brain disease regulating amount of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

The invention will now be illustrated by the following non-limiting examples and with reference to the accompanying Table and Figures.

Example

Measurement of blood pressure in conscious rats by radio-telemetry

Blood pressure was measured using commercially-available radio-telemetry equipment (Data Sciences International, Saint Paul, Minnesota, USA) which provides a means for the remote measurement of the blood pressure (BP), heart rate and activity of a conscious, unrestrained laboratory animal such as a rat. Measurements obtained using this system have the advantage that the test animal is free from stresses induced by surgery and/or restraint.

The equipment comprises a pressure transducer (Code No. TA11PA-C40) (hereinafter the 'pressure transducer implant') that is implanted into the abdomen of a laboratory rat. The transducer transmits a radio signal indicating the pressure in the aorta of the animal and the signal is detected by a receiver (RA1010) placed under the plastic cage which houses the animal. The signal is recorded and evaluated automatically by pre-written computer software (DataQuest 2.1 that may be installed on a suitable computer such as an IBM-compatible personal computer containing an Intel™ 486 processor).

Implantation Methodology

Each of a group of normotensive rats (Alderley Park strain, male animals) was anaesthetised with "Fluothane™" inhalation anaesthetic. The abdomen of each rat was shaved and the skin was coated with a topical disinfectant. An incision was made in the outer skin to expose the abdominal muscle wall which was cut along the mid-line and opened. The viscera of the animal was held back with retractors and the abdominal aorta was located. The aorta was cleaned of connective tissue over a 2-3 cm length and carefully separated from the associated vena cava. Care was taken to ensure that the area of aorta prepared was below the renal arteries to avoid any potential occlusion of the kidneys following surgery. The tip of a 21 gauge needle (Micro Lance, Becton Dickinson) was bent to approximately 90 degrees to the needle shaft. A tie was placed loosely under the aorta. The tie was lifted to occlude the blood vessel and the needle was used to form a puncture into the blood vessel. With the needle held in place in the blood vessel, the bevel of the needle was used carefully to control the insertion of the tip of the catheter from the 'pressure transducer implant' into the blood

vessel. The needle tip was withdrawn and a small drop of surgical glue (Vet Bond 3M) was run down the catheter to form a seal between the catheter and the blood vessel. A cellulose patch was placed over the seal to stabilise the catheter. The 'pressure transducer implant' was stitched into position on the inside of the abdominal wall and the abdominal muscle wall was closed with absorbable stitches. The ends of the stitches were trimmed and the outer skin of the animal was closed using surgical autoclips which were removed 7 days after surgery.

General Study Protocol

The animals were housed in a facility using a 12 hour cycle of light and dark. Normal rat behaviour was seen during the Studies *i.e.* the animals rested during the light phase and were active during the dark phase. Following removal of the surgical autoclips, all rats were handled daily and dosed daily with control vehicle (citrate buffer or 1% polysorbate 80 in water) for a further week in order to acclimatise them to dosing techniques. Blood pressure data were recorded from each animal every 10 minutes throughout each Study. To obtain more reproducible basal blood pressure measurements, data were obtained during the 12 hour light phase when the test animals were inactive.

Typically, on day 1, each of a group of 3 rats was dosed p.o. at approximately 9.00 am with control vehicle and blood pressure data were recorded during the ensuing 24 hour period. The following day, each rat was dosed p.o. at approximately 9.00 am with a suitable dose of a test compound, typically 25 or 12.5 mg/kg, and blood pressure data were recorded during the ensuing 24 hour period. The difference was calculated between the basal blood pressure on day 1 and the basal blood pressure on day 2 following the dosing of the test compound. Both the maximum reduction in blood pressure (in mm Hg) and the time (in hours) for the restoration of normotension were recorded. Illustrative results are shown in Table I where each test compound was administered p.o. at a test dose of 25 mg/kg.

Table I

	Rat telemetry data	
Test Compound	**Hypotensive effect** (mm Hg)	**Return to normotension** (hours)
Src-1	10	7
Src-2	10	8
Src-3	12	24
Src-4	10	25
Src-5	16	20
Src-6	25	23

Notes

Src-1 is the compound 6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-piperidinopropoxy)quinazoline which provides Compound 4 within the Table in Example 2 of International Patent Application WO 02/16352.

Src-2 is the compound 4-(6-chloro-2,3-methylenedioxyanilino)-7-[3-(4-isobutyrylpiperazin-1-yl)propoxy]-6-methoxyquinazoline which provides Compound 34 within the Table in Example 8 of International Patent Application WO 02/16352.

Src-3 is the compound 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline which provides Compound 73 within the Table in Example 14 of International Patent Application WO 01/94341.

Src-4 is the compound 4-(6-chloro-2,3-methylenedioxyanilino)-7-(3-pyrrolidin-1-ylpropoxy)-5-tetrahydropyran-4-yloxyquinazoline which provides Compound 33 within the Table in Example 17 of International Patent Application WO 01/94341.

Src-5 is the compound 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-{2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl)ethoxy]-5-isopropoxyquinazoline which provides Compound 7 within the Table in Example 6 of co-pending European Patent Application No. 02292736.2.

Src-6 is the compound 7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxyquinazoline which provides Compound 6 within the Table in Example 6 of co-pending International Application PCT/GB03/04703 (that arose from European Patent Application No. 02292736.2).

Brief Description of the Drawings

Figure 1 shows the diastolic blood pressure profile following the single dose p.o. at about 9.00 am of control citrate buffer vehicle (thicker line) or of 15 mg/kg of Src-5 (thinner line) with time (minutes) plotted on the horizontal axis and diastolic blood pressure (mm Hg) plotted on the vertical axis.

Figure 2 shows the heart rate profile following the single dose p.o. at about 9.00 am of citrate buffer control vehicle (thicker line) or of 15 mg/kg of Src-5 (thinner line) with time (minutes) plotted on the horizontal axis and the heart rate (beats per minute) plotted on the vertical axis.

The data in the Figures show that at this dose the test compound produces a clear reduction in blood pressure that is accompanied by a reflex tachycardia.

Similar findings were obtained in further telemetered rat experiments when a test compound was administered once daily during a 3 day period. Thus, tachyphylaxis to the multiple administration of a Src kinase inhibitor does not appear to develop.

Similar findings were obtained in telemetered dog experiments. For example, administration of a dose of 10 mg/kg Src-3 produced increases in heart rate but with no overall effect on blood pressure (due to the compensatory tachycardia) whereas dosing at 30 mg/kg produced a clear reduction in blood pressure despite the continuing reflex tachycardia.

Src Inhibitors described within International Application PCT/GB03/04703 (that arose from European Patent Application No. 02292736.2)

Example 1

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-(3-chloropropoxy)-6-methoxyquinazoline

Sodium hexamethyldisilazane (1M solution in THF; 0.734 ml) was added to a solution of 4-amino-5-chloro-2,3-methylenedioxypyridine (0.12 g) in DMF (4 ml) that had been cooled to 0°C and the mixture was stirred for 15 minutes. A portion (0.1 g) of 4-chloro-7-(3-chloropropoxy)-6-methoxyquinazoline was added and the resultant mixture was stirred and allowed to warm to ambient temperature. The mixture was stirred at ambient temperature for 16 hours. The reaction mixture was evaporated and the residue was partitioned between methylene chloride and a saturated aqueous ammonium chloride solution. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and ethyl acetate as eluent followed by increasingly polar mixtures of methylene chloride and acetonitrile. There was thus obtained the title compound as a white foam (0.11 g); NMR Spectrum: ($DMSOd_6$ and CD_3CO_2D) 2.3 (m, 2H), 3.8 (m, 2H), 4.05 (s, 3H), 4.4 (t, 2H), 6.3 (s, 2H), 7.4 (s, 1H), 7.9 (s, 1H), 8.15 (s, 1H), 8.95 (s, 1H); Mass Spectrum: $M+H^+$ 423 and 425.

The 4-amino-5-chloro-2,3-methylenedioxypyridine used as a starting material was prepared as follows :-

Bromochloromethane (20 ml) was added to a mixture 5-chloro-2,3-dihydroxypyridine (30 g), caesium carbonate (100 g) and DMF (300 ml) and the mixture was stirred and heated to 90°C for 3.5 hours. The mixture was cooled to ambient temperature and filtered. The filtrate was evaporated and the residue was purified by column chromatography on silica using methylene chloride as eluent. There was thus obtained 5-chloro-2,3-methylenedioxypyridine as a white solid (4.7 g); NMR Spectrum: ($DMSOd_6$) 6.25 (s, 2H), 7.5 (s, 1H), 7.65 (s, 1H).

A mixture of diisopropylamine (8.2 ml) and THF (100 ml) was cooled to -70°C and n-butyllithium (2.5 M in hexane, 24 ml) was added dropwise. The mixture was stirred at -70°C for a further 20 minutes. A solution of 5-chloro-2,3-methylenedioxypyridine (4.2 g) in THF (40 ml) was added over 10 minutes and the reaction mixture was stirred at -70°C for

1 hour. Dry carbon dioxide gas was bubbled into the reaction mixture for 30 minutes. The resultant reaction mixture was allowed to warm to ambient temperature. Water (20 ml) was added and the organic solvent was evaporated. The residue was acidified to pH2 by the addition of 1N aqueous hydrochloric acid solution. The resultant solid was isolated and washed in turn with water and diethyl ether and dried under vacuum at 40°C. There was thus obtained 5-chloro-2,3-methylenedioxypyridine-4-carboxylic acid (3.6 g); ^{13}C NMR Spectrum: ($DMSOd_6$) 103, 120, 121, 138, 140, 158, 163.

A mixture of the material so obtained, diphenylphosphoryl azide (3.6 ml), anhydrous tert-butanol (13.5 ml), triethylamine (4.2 ml) and 1,4-dioxane (63 ml) was stirred and heated to 100°C for 3 hours. The mixture was evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was washed with water, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 9:1 mixture of methylene chloride and ethyl acetate as eluent. There was thus obtained tert-butyl 5-chloro-2,3-methylenedioxypyrid-4-ylcarbamate (3.8 g); NMR Spectrum: ($DMSOd_6$) 1.45 (s, 9H), 6.2 (s, 2H), 7.7 (s, 1H), 9.2 (s, 1H).

The material so obtained was dissolved in methylene chloride (35 ml) and the solution was cooled to 0°C. Trifluoroacetic acid (15 ml) was added and the mixture was stirred at 0°C for 3 hours. The mixture was allowed to warm to ambient temperature and was stirred for 16 hours. The solvent was evaporated and the residue was diluted with ice water and neutralised to pH7 by the addition of 2N aqueous sodium hydroxide solution whilst keeping the mixture temperature at 0°C. The resultant mixture was extracted with methylene chloride and the extract dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and diethyl ether as eluent. There was thus obtained 4-amino-5-chloro-2,3-methylenedioxypyridine (2 g); NMR Spectrum: ($DMSOd_6$) 6.1 (s, 2H), 6.2 (s, 2H), 7.45 (s, 1H); ^{13}C NMR Spectrum: ($DMSOd_6$) 100, 112, 125, 136, 138, 157; Mass Spectrum: $M+H^+$ 173.

The 4-chloro-7-(3-chloropropoxy)-6-methoxyquinazoline used as a starting material was prepared as follows :-

Ammonium formate (45 g) was added portionwise over 1.25 hours to a stirred mixture of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (International Patent Application WO 02/16352, Example 1 thereof; 20 g), 10% palladium-on-carbon catalyst (3.3 g) and DMF (530 ml) and the reaction mixture was stirred for an additional 30 minutes. The catalyst was removed by filtration and the solvent was evaporated. There was thus obtained 7-hydroxy-

6-methoxy-3,4-dihydroquinazolin-4-one (8.65 g); NMR Spectrum: ($DMSOd_6$) 3.9 (s, 3H), 7.0 (s, 1H), 7.45 (s, 1H), 7.9 (s, 1H).

A mixture of the material so obtained, acetic anhydride (63 ml) and pyridine (7.5 ml) was heated to 100°C for 4.5 hours. The resultant mixture was allowed to stand at ambient temperature for 16 hours. The mixture was poured into a stirred mixture (400 ml) of ice and water. The resultant precipitate was isolated and dried under vacuum. Analysis revealed that hydrolysis of the acetate group on the 4 position of the quinazoline was incomplete. The mixture was therefore further hydrolysed with water (150 ml) and pyridine (a few drops) at 90°C for 15 minutes. The resultant mixture was cooled to ambient temperature and the solid was collected by filtration, washed with water and dried under vacuum. There was thus obtained 7-acetoxy-6-methoxy-3,4-dihydroquinazolin-4-one (7.4 g); NMR Spectrum: ($DMSOd_6$) 2.3 (s, 3H), 3.9 (s, 3H), 7.45 (s, 1H), 7.65 (s, 1H), 8.05 (s, 1H).

A mixture of a portion (2 g) of the material so obtained, thionyl chloride (32 ml) and DMF (5 drops) was stirred and heated to reflux for 1.5 hours. The mixture was cooled to ambient temperature and the excess of thionyl chloride was evaporated. Toluene was added to the residue and evaporated. The resultant residue was diluted with methylene chloride (15 ml) and a 10% ammonia solution in methanol (80 ml) was added and the mixture was heated to 80°C for 10 minutes. The mixture was cooled to ambient temperature and evaporated. Water was added to the residue and the mixture was neutralised by the addition of dilute aqueous hydrochloric acid solution. The resultant precipitate was collected by filtration and dried under vacuum at 35°C for 16 hours. There was thus obtained 4-chloro-7-hydroxy-6-methoxyquinazoline (1.65 g); NMR Spectrum: ($DMSOd_6$) 4.0 (s, 3H), 7.25 (s, 1H), 7.4 (s, 1H), 8.8 (s, 1H).

Di-tert-butyl azodicarboxylate (2.3 g) was added portionwise over a few minutes to a stirred mixture of 4-chloro-7-hydroxy-6-methoxyquinazoline (1.65 g), 3-chloropropanol (0.7 ml), triphenylphosphine (2.6 g) and methylene chloride (100 ml) and the reaction mixture was stirred at ambient temperature for 2 hours. The mixture was concentrated to a volume of about 30 ml by evaporation and the residue was purified by column chromatography on silica using increasingly polar mixtures of petroleum ether (b.p 40-60°C) and ethyl acetate as eluent. There was thus obtained 4-chloro-7-(3-chloropropoxy)-6-methoxyquinazoline as a white solid (2 g); NMR Spectrum: ($DMSOd_6$) 2.3 (m, 2H), 3.8 (m, 2H), 4.05 (s, 3H), 4.4 (m, 2H), 7.45 (s, 1H), 7.55 (s, 1H), 8.9 (s, 1H).

Example 2

7-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-methoxyquinazoline

Using an analogous procedure to that described in Example 1, 4-chloro-7-(2-chloroethoxy)-6-methoxyquinazoline was reacted with 4-amino-5-chloro-2,3-methylenedioxypyridine to give the title compound in 92% yield; NMR Spectrum: ($DMSOd_6$ and CD_3CO_2D) 4.05 (s, 3H), 4.1 (t, 2H), 4.55 (t, 2H), 6.3 (s, 2H), 7.4 (s, 1H), 7.9 (s, 1H), 8.15 (s, 1H), 8.95 (s, 1H); Mass Spectrum: $M+H^+$ 409 and 411.

The 4-chloro-7-(2-chloroethoxy)-6-methoxyquinazoline used as a starting material was prepared as follows :-

1,2-Dichloroethane (400 ml) was added to a stirred mixture of 7-hydroxy-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (International Patent Application WO 02/16352, Example 2, Note [4] thereof; 85 g), potassium carbonate (77 g) and DMF (400 ml) and the reaction mixture was heated to 70°C for 16 hours. The reaction mixture was cooled to ambient temperature and filtered. The filtrate was evaporated and the solid so obtained was washed with water and dried over phosphorus pentoxide at 50°C. The material so obtained was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and ethyl acetate as eluent. There was thus obtained 7-(2-chloroethoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one as a white solid (65.6 g); NMR Spectrum: ($CDCl_3$) 1.2 (s, 9H), 3.9 (t, 2H), 4.0 (s, 3H), 4.4 (t, 2H), 5.95 (s, 2H), 7.1 (s, 1H), 7.7 (s, 1H), 8.2 (s, 1H); Mass Spectrum: $M+H^+$ 369 and 371.

A mixture of the material so obtained and a saturated solution of ammonia gas in methanol (1.6 L) was stirred at ambient temperature for 2 days. The solvent was concentrated by evaporation to about one-fourth of the original volume and the precipitate was collected by filtration and washed with diethyl ether. There was thus obtained 7-(2-chloroethoxy)-6-methoxy-3,4-dihydroquinazolin-4-one as a white solid (44 g); NMR Spectrum: ($DMSOd_6$) 3.9 (s, 3H), 4.05 (t, 2H), 4.4 (t, 2H), 7.15 (s, 1H), 7.45 (s, 1H), 8.0 (s, 1H); Mass Spectrum: $M+H^+$ 255 and 257.

A mixture of a portion (5 g) of the material so obtained, thionyl chloride (28 ml) and DMF (0.7 ml) was stirred and heated to 80°C for 1.5 hours. The excess of thionyl chloride was evaporated and toluene was added and evaporated. The residual solid was suspended in a mixture of ice and water and basified to pH7.5 by the addition of 2N aqueous sodium hydroxide solution followed by a saturated aqueous sodium bicarbonate solution. The

resultant solid was collected by filtration, washed with water and diethyl ether and dried over over phosphorus pentoxide under vacuum. The material so obtained was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and acetonitrile as eluent. There was thus obtained 4-chloro-7-(2-chloroethoxy)-6-methoxyquinazoline (3.06 g; NMR Spectrum: ($CDCl_3$) 3.95 (t, 2H), 4.1 (s, 3H), 4.5 (t, 2H), 7.35 (s, 1H), 7.45 (s, 1H), 8.9 (s, 1H); Mass Spectrum: $M+H^+$ 273 and 275.

Example 3

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-methoxy-7-[3-(4-prop-2-ynylpiperazin-1-yl)propoxy]quinazoline

A mixture of 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-(3-chloropropoxy)-6-methoxyquinazoline (0.08 g), 1-prop-2-ynylpiperazine (0.047 g), potassium iodide (0.01 g) and DMA (2 ml) was stirred and heated to 80°C for 3.5 hours. The solvent was evaporated and the residue was partitioned between methylene chloride and a saturated aqueous ammonium chloride solution. The organic phase was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and methanol and then a 9:1 mixture of methylene chloride and a saturated methanolic ammonia solution as eluent. The resulting gum was triturated under diethyl ether. There was thus obtained the title compound as a solid (0.066 g); NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.3 (m, 2H), 3.2-3.6 (br m, 10H), 3.75 (s, 1H), 3.95 (br s, 2H), 4.0 (s, 3H), 4.35 (m, 2H), 6.3 (s, 2H), 7.4 (s, 1H), 7.9 (s, 1H), 8.15 (s, 1H), 8.95 (s, 1H); Mass Spectrum: $M+H^+$ 511 and 513.

The 1-prop-2-ynylpiperazine used as a starting material was prepared as follows :-

Propargyl bromide (80% solution in toluene; 40 ml) was added dropwise during 10 minutes to a stirred mixture of 1-tert-butoxycarbonylpiperazine (50 g), potassium carbonate (74.2 g) and acetonitrile (2 L) that had been cooled to 0°C. The mixture was stirred for 1.5 hours and allowed to warm to ambient temperature. The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and ethyl acetate as eluent. There was thus obtained tert-butyl 4-prop-2-ynylpiperazine-1-carboxylate as an oil (45.5 g); NMR Spectrum: ($CDCl_3$) 1.4 (s, 9H), 2.2 (s, 1H), 2.45 (m, 4H), 3.3 (s, 2H), 3.45 (m, 4H).

A solution of the material so obtained in methylene chloride (100 ml) was added slowly to a solution of hydrogen chloride gas in 1,4-dioxane (4M, 450 ml). The reaction was

slightly exothermic and a precipitate formed as carbon dioxide gas was evolved. The mixture was stirred at ambient temperature for 1 hour. The resultant mixture was evaporated and the residue was suspended in methylene chloride. A solution of ammonia gas in methanol (7M, 110 ml) was added and the mixture was stirred at ambient temperature for 15 minutes. The mixture was filtered and the filtrate was evaporated. An oil was obtained which crystallised on standing. There was thus obtained 1-prop-2-ynylpiperazine (23 g); NMR Spectrum: ($CDCl_3$) 2.2 (s, 1H), 2.5 (br s, 4H), 2.85 (m, 4H), 3.25 (s, 2H).

Example 4

7-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-tetrahydropyran-4-yloxyquinazoline

Using an analogous procedure to that described in Example 1, 4-chloro-7-(2-chloroethoxy)-5-tetrahydropyran-4-yloxyquinazoline was reacted with 4-amino-5-chloro-2,3-methylenedioxypyridine to give the title compound in 37% yield; NMR Spectrum: ($CDCl_3$) 2.0 (m, 2H), 2.3 (m, 2H), 3.65 (m, 2H), 3.9 (m, 2H), 4.1 (m, 2H), 4.4 (m, 2H), 4.8 (m, 1H), 6.2 (s, 2H), 6.65 (s, 1H), 6.9 (s, 1H), 7.8 (s, 1H), 8.6 (s, 1H), 9.5 (s, 1H); Mass Spectrum: $M+H^+$ 479 and 481.

The 4-chloro-7-(2-chloroethoxy)-5-tetrahydropyran-4-yloxyquinazoline used as a starting material was prepared as follows :-

Di-tert-butyl azodicarboxylate (0.338 g) was added to a stirred mixture of 4-chloro-7-hydroxy-5-tetrahydropyran-4-yloxyquinazoline (International Patent Application WO 01/94341, Example 15, Note [10] thereof; 0.25 g), 2-chloroethanol (0.073 ml), triphenylphosphine (0.385 g) and methylene chloride (15 ml) and the reaction mixture was stirred at ambient temperature for 1 hour. The mixture was concentrated to a volume of about 5 ml by evaporation and the residue was purified by column chromatography on silica using increasingly polar mixtures of petroleum ether (b.p 40-60°C) and ethyl acetate as eluent. There was thus obtained 4-chloro-7-(2-chloroethoxy)-5-tetrahydropyran-4-yloxyquinazoline as a solid (0.17 g); NMR Spectrum: ($CDCl_3$) 2.0 (m, 2H), 2.15 (m, 2H), 3.7 (m, 2H), 3.95 (t, 2H), 4.1 (m, 2H), 4.4 (t, 2H), 4.8 (m, 1H), 6.7 (s, 1H), 6.95 (s, 1H), 8.85 (s, 1H).

Example 5

7-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxyquinazoline

Using an analogous procedure to that described in Example 1, 4-chloro-7-(2-chloroethoxy)-5-isopropoxyquinazoline was reacted with 4-amino-5-chloro-2,3-methylenedioxypyridine to give the title compound in 86% yield; NMR Spectrum: ($CDCl_3$) 1.55 (d, 6H), 3.9 (t, 2H), 4.4 (t, 2H), 4.9 (m, 1H), 6.2 (s, 2H), 6.6 (s, 1H), 6.85 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.65 (s, 1H); Mass Spectrum: $M+H^+$ 437 and 439.

The 4-chloro-7-(2-chloroethoxy)-5-isopropoxyquinazoline used as a starting material was prepared as follows :-

Di-tert-butyl azodicarboxylate (28.9 g) was added to a stirred mixture of 7-benzyloxy-5-hydroxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (International Patent Application WO 01/94341, Example 15, Note [8] thereof; 30 g), isopropanol (7.3 ml), triphenylphosphine (32.95 g) and methylene chloride (350 ml) that had been cooled to 0°C. The reaction mixture was allowed to warm to ambient temperature and was stirred for 1.5 hours. The mixture was evaporated and the residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained 7-benzyloxy-5-isopropoxy-3,4-dihydroquinazolin-4-one as a solid (23.8 g); NMR Spectrum: ($DMSOd_6$) 7.89 (s, 1H), 7.5-7.3 (m, 5H), 6.75 (s, 1H), 6.62 (s, 1H), 5.24 (s, 2H), 4.65 (m, 1H), 1.29 (d, 6H).

Ammonium formate (48.4 g) was added to a stirred mixture of 7-benzyloxy-5-isopropoxy-3,4-dihydroquinazolin-4-one (23.8 g), 10% palladium-on-carbon catalyst (2.8 g) and DMF (300 ml) and the resultant mixture was stirred at ambient temperature for 2 hours. The mixture was filtered and the filtrate was evaporated. The material so obtained was triturated under water, the pH of which was adjusted to pH7. The solid so obtained was collected by filtration, washed with water and with diethyl ether and dried over phosphorus pentoxide under vacuum. There was thus obtained 7-hydroxy-5-isopropoxy-3,4-dihydroquinazolin-4-one as a white solid (15.9 g); NMR Spectrum: ($DMSOd_6$) 1.3 (d, 6H), 4.57 (m, 1H), 6.42 (s, 1H), 6.5 (s, 1H), 7.8 (s, 1H).

A mixture of the material so obtained, acetic anhydride (34 ml) and pyridine (0.62 ml) was heated to 70°C for 30 minutes. The reaction mixture was cooled to ambient temperature and the excess of acetic anhydride was evaporated. The white solid so obtained was added to hot water (80°C, 250 ml) and the mixture was stirred vigorously

and heated to 80°C for 20 minutes. The mixture was cooled to ambient temperature and the solid was isolated and dried over phosphorus pentoxide. There was thus obtained 7-acetoxy-5-isopropoxy-3,4-dihydroquinazolin-4-one (17.86 g); NMR Spectrum: ($DMSOd_6$) 7.97 (s, 1H), 6.91 (s, 1H), 6.85 (s, 1H), 4.65 (m, 1H), 2.32 (s, 3H), 1.33 (d, 6H).

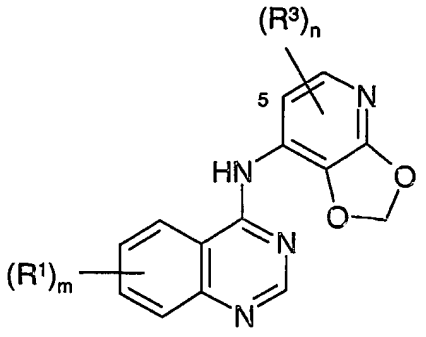
A mixture of a portion (5.4 g) of the material so obtained, triphenylphosphine (10.8 g), carbon tetrachloride (12 ml) and 1,2-dichloroethane (50 ml) was stirred and heated to 70°C for 2 hours. The mixture was cooled to ambient temperature and the solvent was evaporated. The residue was dissolved in a 0.5M solution of ammonia gas in 1,4-dioxane (250 ml) and the mixture was heated to 70°C for 10 minutes. The solvent was evaporated and the residue was cooled in an ice-water bath. Methylene chloride and water were added and the aqueous layer was brought to pH7 by the addition of dilute aqueous hydrochloric acid. The mixture was filtered. The organic phase was dried over magnesium sulphate and evaporated to give 4-chloro-7-hydroxy-5-isopropoxyquinazoline as a foam which was used without further purification.

Di-tert-butyl azodicarboxylate (7.9 g) was added to a stirred mixture of the 4-chloro-7-hydroxy-5-isopropoxyquinazoline so obtained, 2-chloroethanol (1.5 ml), triphenylphosphine (8 g) and methylene chloride (200 ml) and the reaction mixture was stirred at ambient temperature for 4 hours. The mixture was concentrated by evaporation and the residue was purified by column chromatography on silica using increasingly polar mixtures of petroleum ether (b.p 40-60°C) and ethyl acetate as eluent. There was thus obtained 4-chloro-7-(2-chloroethoxy)-5-isopropoxyquinazoline (2.5 g); NMR Spectrum: ($CDCl_3$) 1.45 (d, 6H), 3.9 (t, 2H), 4.4 (t, 2H), 4.75 (m, 1H), 6.65 (s, 1H), 6.9 (s, 1H), 8.8 (s, 1H).

Example 6

Using an analogous procedure to that described in Example 3, the appropriate 7-haloalkoxyquinazoline was reacted with the appropriate heterocyclic compound to give the compounds described in Table I. Unless otherwise stated, each compound described in Table I was obtained as a free base.

Table I



Compound No. & Note	$(R^1)_m$	$(R^3)_n$
[1]	6-methoxy-7-[3-(4-isobutyrylpiperazin-1-yl)propoxy]	5-chloro
[2]	6-methoxy-7-{3-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]propoxy}	5-chloro
[3]	6-methoxy-7-[2-(4-prop-2-ynylpiperazin-1-yl)ethoxy]	5-chloro
[4]	5-tetrahydropyran-4-yloxy-7-[2-(4-acetylpiperazin-1-yl)ethoxy]	5-chloro
[5]	5-tetrahydropyran-4-yloxy-7-{2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]ethoxy}	5-chloro
[6]	5-isopropoxy-7-[2-(4-acetylpiperazin-1-yl)ethoxy]	5-chloro
[7]	5-isopropoxy-7-{2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]ethoxy}	5-chloro

Notes

[1] The reactants were 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-(3-chloropropoxy)-6-methoxyquinazoline and 1-isobutyrylpiperazine. The reaction mixture was heated to 120°C for 3 hours. The reaction product was purified by column chromatography on a C18 reversed phase silica column (Waters Symmetry column, 5 microns silica, 19 mm diameter, 100 mm length) using a decreasingly polar mixture of water and acetonitrile (containing 1% acetic acid) as eluent. The material so obtained was dissolved in methylene chloride and an ion exchange resin (diethylaminopolystyrene resin, 4 equivalents) was added and the mixture was stirred for 30 minutes. The mixture was

filtered and the filtrate was evaporated. The resultant residue was triturated under pentane to give the required product in 51% yield which gave the following characterising data; NMR Spectrum: ($CDCl_3$) 1.1 (d, 6H), 2.1 (m, 2H), 2.45 (m, 4H), 2.55 (m, 2H), 2.75 (m, 1H), 3.5 (m, 2H), 3.6 (m, 2H), 4.0 (s, 3H), 4.25 (t, 2H), 6.1 (s, 2H), 7.1 (br s, 1H), 7.3 (s, 1H), 7.75 (s, 1H), 8.7 (br s, 1H); Mass Spectrum: $M+H^+$ 543 and 545.

The 1-isobutyrylpiperazine used as a starting material was prepared as follows :-

Isobutyryl chloride (3.25 ml) was added dropwise to a stirred mixture of 1-benzylpiperazine (5 g), triethylamine (4.35 ml) and methylene chloride (75 ml) which was cooled to 0°C. The reaction mixture was allowed to warm to ambient temperature and stirred for 1 hour. The mixture was partitioned between methylene chloride and water. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 3:2 mixture of methylene chloride and ethyl acetate as eluent. There was thus obtained 1-benzyl-4-isobutyrylpiperazine (5.95 g) as an oil; NMR Spectrum: ($CDCl_3$) 1.1 (d, 6H), 2.45 (m, 4H), 2.8 (m, 1H), 3.5 (m, 4H), 3.65 (m, 2H), 7.3 (m, 5H); Mass Spectrum: $M+H^+$ 247.

A mixture of the material so obtained, cyclohexene (70 ml), palladium oxide-on-carbon catalyst (20%; 1.1 g) and ethanol (120 ml) was stirred and heated to 80°C for 3 hours. The catalyst was removed by filtration and the solvent was evaporated to give 1-isobutyrylpiperazine (3.7 g) as a solid; NMR Spectrum: ($CDCl_3$) 1.05 (d, 6H), 2.75 (m, 1H), 2.8 (m, 4H), 3.45 (m, 2H), 3.55 (m, 2H).

[2] The reactants were 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-(3-chloropropoxy)-6-methoxyquinazoline and 1-(2,2,2-trifluoroethyl)piperazine. The reaction mixture was heated to 120°C for 3 hours. The reaction product was purified by column chromatography on a C18 reversed phase silica column (Waters Symmetry column, 5 microns silica, 19 mm diameter, 100 mm length) using a decreasingly polar mixture of water and acetonitrile (containing 1% acetic acid) as eluent. The material so obtained was dissolved in methylene chloride and an ion exchange resin (diethylaminopolystyrene resin, 4 equivalents) was added and the mixture was stirred for 30 minutes. The mixture was filtered and the filtrate was evaporated. The resultant residue was triturated under pentane to give the required product in 72% yield which gave the following characterising data; NMR Spectrum: ($CDCl_3$) 2.1 (m, 2H), 2.5 (m, 6H), 2.7 (m, 4H), 2.95 (q, 2H), 4.05 (s, 3H), 4.25 (t, 2H), 6.1 (s, 2H), 7.1 (br s, 1H), 7.3 (s, 1H), 7.75 (s, 1H), 8.35 (br s, 1H); Mass Spectrum:

$M+H^+$ 555 and 557; Elemental Analysis: Found C, 51.8; H, 5.0; N, 14.8; $C_{24}H_{26}ClF_3N_6O_4$ requires C, 51.9; H, 4.7; N, 15.1%.

The 1-(2,2,2-trifluoroethyl)piperazine used as a starting material was prepared as follows :-

2,2,2-Trifluoroethyl trifluoromethanesulphonate (8.2 g) was added to a stirred mixture of 1-tert-butoxycarbonylpiperazine (6 g), potassium carbonate (5.77 g) and acetonitrile (30 ml) and the resultant mixture was stirred at ambient temperature for 16 hours. The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of petroleum ether (b.p 40-60°C) and ethyl acetate as eluent. There was thus obtained tert-butyl 4-(2,2,2-trifluoroethylpiperazine-1-carboxylate as a solid (8.1 g); NMR Spectrum: ($CDCl_3$) 1.45 (s, 9H), 2.6 (m, 4H), 2.95 (q, 2H), 3.4 (m, 4H).

Hydrogen chloride gas was bubbled through a solution of tert-butyl 4-(2,2,2-trifluoroethylpiperazine-1-carboxylate (8 g) in ethyl acetate (50 ml) during 1.5 hours. A precipitate formed as carbon dioxide gas was evolved. The precipitate was collected by filtration, washed with ethyl acetate and dried under vacuum. There was thus obtained 1-(2,2,2-trifluoroethyl)piperazine hydrochloride (7 g); NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.85 (m, 4H), 3.1 (m, 4H), 3.35 (q, 2H).

The material so obtained was suspended in methylene chloride and a saturated methanolic ammonia solution (20 ml) was added. The resultant mixture was stirred at ambient temperature for 20 minutes. The mixture was filtered and the filtrate was evaporated at ambient temperature under vacuum. There was thus obtained 1-(2,2,2-trifluoroethyl)piperazine which was used without any additional purification.

[3] The reactants were 7-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-methoxyquinazoline and 1-prop-2-ynylpiperazine. The required product was obtained in 52% yield and gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CD_3CO_2D) 3.3 (br s, 4H), 3.6 (br s, 4H), 3.75 (br s, 3H), 3.95 (s, 2H), 4.05 (s, 3H), 4.65 (t, 2H), 6.3 (s, 2H), 7.5 (s, 1H), 7.9 (s, 1H), 8.2 (s, 1H), 9.0 (s, 1H); Mass Spectrum: $M+H^+$ 497 and 499; Elemental Analysis: Found C, 56.3; H, 5.4; N, 16.2; $C_{24}H_{25}ClN_6O_4$ $0.7H_2O$ requires C, 56.6; H, 5.2; N, 16.5%.

[4] The reactants were 7-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-tetrahydropyran-4-yloxyquinazoline and 1-acetylpiperazine. The reaction mixture was heated to 80°C for 3 hours and then to 110°C for 5 hours. The reaction product

was purified by column chromatography on a C18 reversed phase silica column (Waters Symmetry column, 5 microns silica, 19 mm diameter, 100 mm length) using a decreasingly polar mixture of water and acetonitrile (containing 1% acetic acid) as eluent. The organic solvents were evaporated and the pH of the aqueous phase was adjusted to 7.5. The solution was extracted with methylene chloride and the organic phase was dried over magnesium sulphate and evaporated. The resultant residue was triturated under diethyl ether to give the required product in 45% yield which gave the following characterising data; NMR Spectrum: ($CDCl_3$) 2.0 (m, 2H), 2.1 (s, 3H), 2.3 (m, 2H), 2.6 (m, 4H), 2.95 (m, 2H), 3.55 (m, 2H), 3.65 (m, 4H), 4.1 (m, 2H), 4.3 (m, 2H), 4.8 (m, 1H), 6.2 (s, 2H), 6.6 (s, 1H), 6.9 (s, 1H), 7.8 (s, 1H), 8.65 (s, 1H), 9.5 (s, 1H); Mass Spectrum: $M+H^+$ 571 and 573; Elemental Analysis: Found C, 55.3; H, 5.4; N, 13.9; $C_{27}H_{31}ClN_6O_6$ $1H_2O$ requires C, 55.1; H, 5.7; N, 14.3.

[5] The reactants were 7-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-tetrahydropyran-4-yloxyquinazoline and (3RS,4SR)-3,4-methylenedioxypyrrolidine. The reaction mixture was heated to 80°C for 3 hours and then to 110°C for 5 hours. The reaction product was purified by column chromatography on a C18 reversed phase silica column (Waters Symmetry column, 5 microns silica, 19 mm diameter, 100 mm length) using a decreasingly polar mixture of water and acetonitrile (containing 1% acetic acid) as eluent. The organic solvents were evaporated and the pH of the aqueous phase was adjusted to 7.5. The solution was extracted with methylene chloride and the organic phase was dried over magnesium sulphate and evaporated. The resultant residue was triturated under diethyl ether to give the required product in 69% yield which gave the following characterising data; NMR Spectrum: ($CDCl_3$) 2.0 (m, 2H), 2.3 (m, 2H), 2.4 (m, 2H), 2.3 (t, 2H), 3.3 (d, 2H), 3.55 (m, 2H), 4.1 (m, 2H), 4.3 (t, 2H), 4.65 (m, 2H), 4.8 (m, 1H), 4.9 (s, 1H), 5.2 (s, 1H), 6.2 (s, 2H), 6.6 (s, 1H), 6.9 (s, 1H), 7.8 (s, 1H), 8.65 (s, 1H), 9.5 (s, 1H); Mass Spectrum: $M+H^+$ 558 and 560; Elemental Analysis: Found C, 56.5; H, 5.3; N, 12.5; $C_{26}H_{28}ClN_5O_7$ $0.2Et_2O$ requires C, 56.2; H, 5.3; N, 12.2%.

The (3RS,4SR)-3,4-methylenedioxypyrrolidine used as a starting material was prepared as follows :-

A solution of di-tert-butyl dicarbonate (Boc_2O, 78.95 g) in ethyl acetate (125 ml) was added dropwise to a stirred mixture of 3-pyrroline (25 g; 65% pure containing pyrrolidine) and ethyl acetate (125 ml) which had been cooled to 0°C. The reaction temperature was maintained at 5-10°C during the addition. The resultant reaction mixture was allowed to warm to ambient temperature overnight. The reaction mixture

was washed successively with water, 0.1N aqueous hydrochloric acid solution, water, a saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and evaporated. There was thus obtained, as a colorless oil (62 g), a 2:1 mixture of tert-butyl 3-pyrroline-1-carboxylate, NMR: ($CDCl_3$) 1.45 (s, 9H), 4.1 (d, 4H), 6.75 (m, 2H), and tert-butyl pyrrolidine-1-carboxylate, NMR: ($CDCl_3$) 1.5 (s, 9H), 1.8 (br s, 4H), 3.3 (br s, 4H).

A solution of the mixture of materials so obtained in acetone (500 ml) was added dropwise to a mixture of N-methylmorpholine-N-oxide (28.45 g), osmium tetroxide (1 g) and water (500 ml) whilst keeping the reaction temperature below 25°C. The reaction mixture was then stirred at ambient temperature for 5 hours. The solvent was evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was washed with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of petroleum ether (b.p. 40-60°C) and ethyl acetate as eluent and by further column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol. There was thus obtained tert-butyl (3RS,4SR)-3,4-dihydroxypyrrolidine-1-carboxylate as an oil (34.6 g); NMR Spectrum: ($CDCl_3$) 1.45 (s, 9H), 2.65 (m, 2H), 3.35 (m, 2H), 3.6 (m, 2H), 4.25 (m, 2H).

A solution of tert-butyl (3RS,4SR)-3,4-dihydroxypyrrolidine-1-carboxylate (34.6 g) in DMF (400 ml) was cooled to 0-5°C and sodium hydride (60% dispersion in mineral oil, 0.375 mol) was added portionwise. The reaction mixture was stirred at 5°C for 1 hour. Dibromomethane (15.6 ml) was added and the reaction mixture was stirred at 5°C for 30 minutes. The reaction mixture was allowed to warm to ambient temperature and was stirred for 16 hours. The DMF was evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of petroleum ether (b.p. 40-60°C) and ethyl acetate as eluent. There was thus obtained tert-butyl (3RS,4SR)-3,4-methylenedioxypyrrolidine-1-carboxylate as a colourless oil (19.77 g);NMR Spectrum: ($CDCl_3$) 1.45 (s, 9H), 3.35 (m, 2H), 3.75 (br s, 2H), 4.65 (m, 2H), 4.9 (s, 1H), 5.1 (s, 1H).

A cooled 5M solution of hydrogen chloride in isopropanol (150 ml) was added to a solution of tert-butyl (3RS,4SR)-3,4-methylenedioxypyrrolidine-1-carboxylate (19.7 g) in methylene chloride (500 ml) that was cooled in an ice bath. The reaction mixture was allowed to warm to ambient temperature and was stirred for 4 hours. The solvent was evaporated and

the residue was triturated under diethyl ether. The precipitate was collected by filtration, washed with diethyl ether and dried. There was thus obtained (3RS,4SR)-3,4-methylenedioxypyrrolidine hydrochloride as a beige solid (13.18 g); NMR Spectrum: ($DMSOd_6$) 3.15 (m, 2H), 3.35 (m, 2H), 4.65 (s, 1H), 4.8 (m, 2H), 5.1 (s, 1H).

The material so obtained was suspended in diethyl ether and a saturated methanolic ammonia solution was added. The resultant mixture was stirred at ambient temperature for 10 minutes. The mixture was filtered and the solvent was evaporated at ambient temperature under vacuum. There was thus obtained (3RS,4SR)-3,4-methylenedioxypyrrolidine which was used without any additional purification.

[6] The reactants were 7-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxyquinazoline and 1-acetylpiperazine. The reaction mixture was heated to 85°C for 8 hours. The reaction product was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. The product was obtained in 89% yield and gave the following characterising data; NMR Spectrum: ($CDCl_3$) 1.55 (d, 6H), 2.1 (s, 3H), 2.6 (m, 4H), 2.9 (t, 2H), 3.5 (t, 2H), 3.7 (t, 2H), 4.25 (t, 2H), 4.85 (m, 1H), 6.15 (s, 2H), 6.55 (s, 1H), 6.85 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.6 (s, 1H); Mass Spectrum: $M+H^+$ 529 and 531; Elemental Analysis: Found C, 57.0; H, 5.71; N, 15.7; $C_{25}H_{29}ClN_6O_5$ requires C, 56.8; H, 5.5; N, 15.9%.

[7] The reactants were 7-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxyquinazoline and (3RS,4SR)-3,4-methylenedioxypyrrolidine. The reaction mixture was heated to 95°C for 3 hours. The reaction product was purified by column chromatography on a C18 reversed phase silica column (Waters Symmetry column, 5 microns silica, 19 mm diameter, 100 mm length) using a decreasingly polar mixture of water and acetonitrile (containing 1% acetic acid) as eluent. The organic solvents were evaporated and the pH of the aqueous phase was adjusted to 7. The solution was extracted with methylene chloride and the organic phase was dried over magnesium sulphate and evaporated. The resultant residue was triturated under diethyl ether to give the required product in 64% yield which gave the following characterising data; NMR Spectrum: ($CDCl_3$) 1.55 (d, 6H), 2.35 (m, 2H), 2.9 (t, 2H), 3.25 (d, 2H), 4.25 (t, 2H), 4.6 (m, 2H), 4.85 (m, 1H), 4.9 (s, 1H), 5.15 (s, 1H), 6.15 (s, 2H), 6.55 (s, 1H), 6.85 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.6 (s, 1H); Mass Spectrum: $M+H^+$ 516 and 518; Elemental Analysis: Found C, 54.7; H, 5.2; N, 13.2; $C_{24}H_{26}ClN_5O_6$ $0.5H_2O$ requires C, 54.9; H, 5.2; N, 13.3%.

CLAIMS

1. The use of a compound that is an inhibitor of one of more of the members of the Src family of non-receptor tyrosine kinase enzymes, or a pharmaceutically-acceptable salt thereof, in the production of a medicament for use in the prophylaxis or treatment of hypertension.

2. The use according to claim 1 of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, wherein the Src kinase inhibitor possesses selective kinase inhibitory properties.

3. The use of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, according to claim 1, wherein the Src kinase inhibitor possesses substantially better potency against the Src family of non-receptor tyrosine kinases than against VEGF receptor tyrosine kinases.

4. The use of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, according to claim 1 wherein the Src kinase inhibitor is described in International Patent Applications WO 01/94341 or WO 02/16352 or in co-pending International Application PCT/GB03/04703 (that arose from European Patent Application No. 02292736.2).

5. The use of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, according to claim 1 in the production of a medicament for chronic administration for the prophylaxis or treatment of hypertension.

6. The use of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, according to claim 1 in the production of a medicament for chronic administration wherein the Src kinase inhibitor possesses one or more of the following pharmacokinetic parameters :-

(i) Compound Clearance of less than about 75% of hepatic blood flow;

(ii) a Volume of Distribution of less than about 30 L/kg;

(iii) a bioavailability of more than about 20%; and

(iv) an elimination half life in the range of about 0.2 to 15 hours.

7. The use of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, according to claim 1 in the production of a medicament for chronic administration for the prophylaxis or treatment of hypertension wherein the Src kinase inhibitor possesses substantially better potency against the Src family of non-receptor tyrosine kinases than against VEGF receptor tyrosine kinases.

8. The use of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, according to claim 7 wherein the Src kinase inhibitor is described in International Patent Applications WO 01/94341 or WO 02/16352 or in co-pending International Application PCT/GB03/04703 (that arose from European Patent Application No. 02292736.2).

9. The use according to claim 1 of a Src kinase inhibitor selected from :-
4-(2,4-dichloro-5-methoxyanilino)-7-(2-piperidinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline,
4-(2,4-dichloro-5-methoxyanilino)-7-(2-morpholinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline,
4-(2,4-dichloro-5-methoxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline,
4-(2-bromo-5-methoxyanilino)-7-(2-pyrrolidin-1-ylethoxy)-5-tetrahydropyran-4-yloxyquinazoline,
4-(6-chloro-2,3-methylenedioxyanilino)-7-(2-pyrrolidin-1-ylethoxy)-5-tetrahydropyran-4-yloxyquinazoline,
4-(6-chloro-2,3-methylenedioxyanilino)-7-(3-pyrrolidin-1-ylpropoxy)-5-tetrahydropyran-4-yloxyquinazoline,
4-(6-chloro-2,3-methylenedioxyanilino)-7-[3-(4-methylpiperazin-1-yl)propoxy]-5-tetrahydropyran-4-yloxyquinazoline,
4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline,
4-(6-chloro-2,3-methylenedioxyanilino)-7-(2-piperidinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline,
6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-morpholinopropoxy)quinazoline,
6-methoxy-4-(2,3-methylenedioxyanilino)-7-[3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy]quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,
6-methoxy-4-(2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]quinazoline,
6-methoxy-4-(2,3-methylenedioxyanilino)-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,
6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-piperidinopropoxy)quinazoline,
4-(6-chloro-2,3-methylenedioxyanilino)-7-[3-(4-isobutyrylpiperazin-1-yl)propoxy]-6-methoxyquinazoline,
4-(2-chloro-5-methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline,
4-(2-chloro-5-methoxyanilino)-6-methoxy-7-piperidin-4-ylmethoxyquinazoline,
4-(2-bromo-5-methoxyanilino)-6-methoxy-7-[2-(N-methylpiperidin-4-yl)ethoxy]quinazoline,
4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline,
4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-piperidin-4-ylmethoxyquinazoline,
4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-[2-(N-methylpiperidin-4-yl)ethoxy]quinazoline,
4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-methoxy-7-[3-(4-prop-2-ynylpiperazin-1-yl)propoxy]quinazoline,
7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-tetrahydropyran-4-yloxyquinazoline,
4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-{2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline,
7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxyquinazoline and
4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-{2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl)ethoxy]-5-isopropoxyquinazoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

10. The use according to claim 1 of a Src kinase inhibitor selected from :-
4-(2,4-dichloro-5-methoxyanilino)-7-(2-piperidinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline,
4-(2,4-dichloro-5-methoxyanilino)-7-(2-morpholinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline,
4-(6-chloro-2,3-methylenedioxyanilino)-7-(2-pyrrolidin-1-ylethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-(3-pyrrolidin-1-ylpropoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-(2-piperidinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-morpholinopropoxy)quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-piperidinopropoxy)quinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-[3-(4-isobutyrylpiperazin-1-yl)propoxy]-6-methoxyquinazoline,

4-(2-chloro-5-methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline,

4-(2-chloro-5-methoxyanilino)-6-methoxy-7-piperidin-4-ylmethoxyquinazoline,

4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline,

4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-piperidin-4-ylmethoxyquinazoline,

7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-tetrahydropyran-4-yloxyquinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-{2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline,

7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxyquinazoline and

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-{2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl)ethoxy]-5-isopropoxyquinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

11. The use according to claim 1 of a Src kinase inhibitor selected from :-

4-(6-chloro-2,3-methylenedioxyanilino)-7-(2-pyrrolidin-1-ylethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-(3-pyrrolidin-1-ylpropoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-(2-piperidinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-morpholinopropoxy)quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-piperidinopropoxy)quinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-[3-(4-isobutyrylpiperazin-1-yl)propoxy]-6-methoxyquinazoline,

4-(2-chloro-5-methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline,

7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-tetrahydropyran-4-yloxyquinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-{2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline,

7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxyquinazoline and

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-{2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl)ethoxy]-5-isopropoxyquinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

12. A method for the prophylaxis or treatment of hypertension in a warm-blooded animal such as man which comprises the administration of an effective anti-hypertensive amount of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof.

13. A method for the prophylaxis or treatment of hypertension according to claim 12 wherein the Src kinase inhibitor possesses selective kinase inhibitory properties.

14. A method for the prophylaxis or treatment of hypertension according to claim 12 wherein the Src kinase inhibitor possesses substantially better potency against the Src family of non-receptor tyrosine kinases than against VEGF receptor tyrosine kinases.

15. A method for the prophylaxis or treatment of hypertension according to claim 12 wherein the Src kinase inhibitor is described in International Patent Applications WO 01/94341

or WO 02/16352 or in co-pending International Application PCT/GB03/04703 (that arose from European Patent Application No. 02292736.2).

16. A method for the prophylaxis or treatment of hypertension according to claim 12 which comprises the chronic administration of an effective anti-hypertensive amount of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof.

17. A combination product comprising a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, according to any one of claims 1 to 11 and one or more further anti-hypertensive agents for use in the prophylaxis or treatment of hypertension.

18. A pharmaceutical composition for use in the prophylaxis or treatment of hypertension which comprises a combination product according to claim 17 in association with a pharmaceutically-acceptable excipient or carrier.

19. The use of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, according to any one of claims 1 to 11 in the production of a medicament for the primary regulation of diseases of the cardiovascular system.

20. A method for the primary regulation of diseases of the cardiovascular system in a warm-blooded animal such as man which comprises the administration of an effective cardiovascular regulating amount of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, according to any one of claims 1 to 11.

21. The use of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, according to any one of claims 1 to 11 in the production of a medicament for use in the prevention of brain disease such as stroke.

22. A method for the prevention of brain disease such as stroke in a warm-blooded animal such as man which comprises the administration of an effective brain disease regulating amount of a Src kinase inhibitor, or a pharmaceutically-acceptable salt thereof, according to any one of claims 1 to 11.

Figure 1

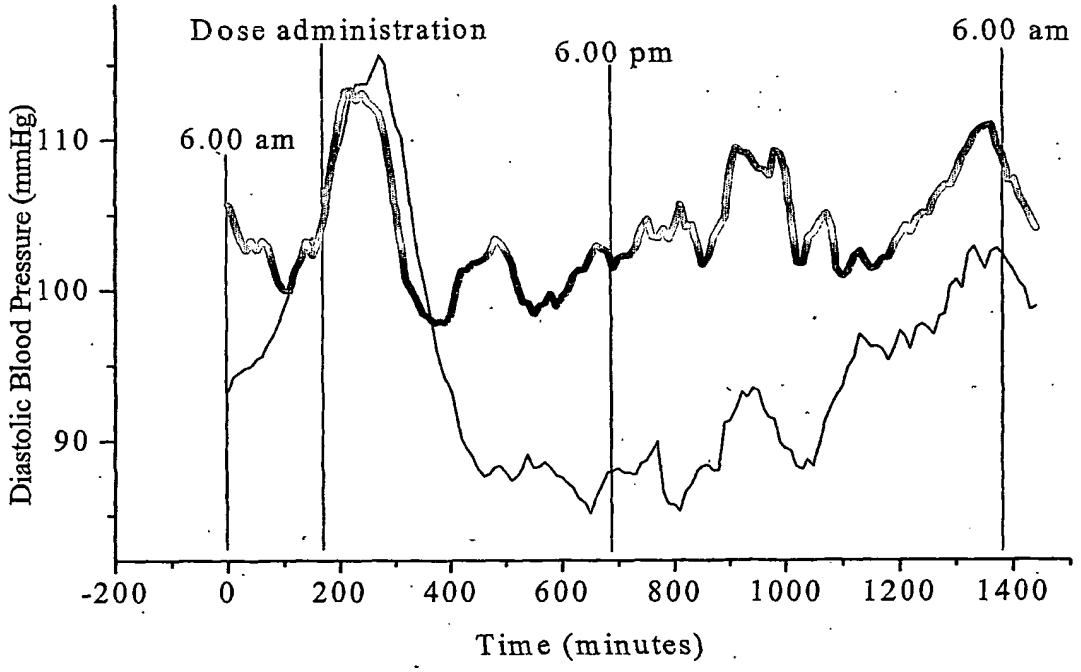


Figure 1/2 effect of Src-5 on rat diastolic blood pressure

Figure 2

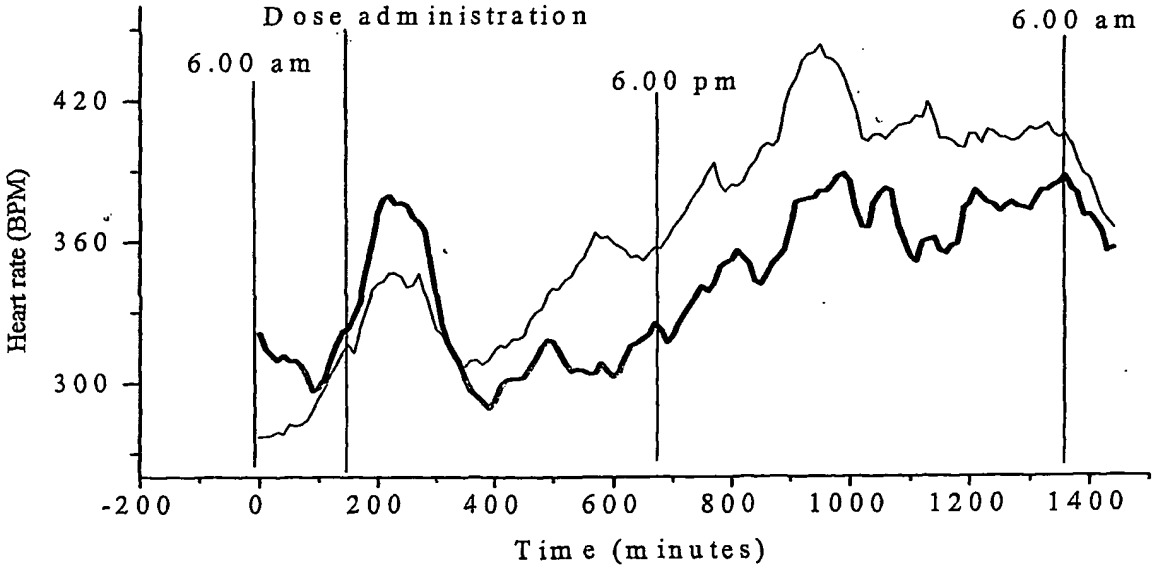


Figure 2/2 effect of Src-5 on rat heart rate